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BY THE COMPTROLLER GENERAL

Report To The Congress

OF THE UNITED STATES

Regulation Of Cancer-Causing Food Additives – Time For A Change?

The 1958 "Delaney Clause" of the Federal Food, Drug, and Cosmetic Act, which requires the Food and Drug Administration to ban the use of cancer-causing food additives, continues to be a source of controversy, an emotional issue, and a target for change.

While food safety experts agree that the Delaney Clause should be changed because of its inflexibility, they disagree on the regulatory alternatives that should replace it.

This report discusses the views of experts on this matter, the scientific tests used as a basis for decisionmaking, and the manner in which different agencies regulate cancer-causing substances. It also presents several alternative decisionmaking frameworks for the Congress to consider.

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COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON D.C. 20548

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To the President of the Senate and the
Speaker of the House of Representatives

This report discusses the Delaney Clause, which was incorporated into the Federal Food, Drug, and Cosmetic Act by the Food Additives Amendment of 1958. The Clause requires the Food and Drug Administration to ban food additives which are found to cause cancer when ingested by humans or animals or are found, after tests which evaluate the safety of food additives, to induce cancer in humans or animals. We made this review at the request of seven Members of Congress to determine if modifications were needed to the Delaney Clause and to present an overview of the social, scientific, and regulatory issues involving food additives that may cause cancer.

We are sending copies of this report to the Director, Office of Management and Budget; the Secretaries of Health and Human Services and Labor; the Administrator, Environmental Protection Agency; and the Chairman, Consumer Product Safety Commission.

Charles A. Bowsher

Comptroller General
of the United States

COMPTROLLER GENERAL'S REPORT TO THE CONGRESS

REGULATION OF CANCER-CAUSING FOOD ADDITIVES--TIME FOR A CHANGE?

D I G E S T

Recent debates over the safety and regulation of saccharin and nitrite have increased public concern about the use of food additives, particularly the possibility that some might cause cancer.

About 2,700 food additives and 33 color additives used in food are regulated by the Food and Drug Administration (FDA). These substances are used to preserve, color, flavor, and aid in processing food or maintaining its nutritional quality.

WHY THE REVIEW WAS MADE

In response to a request from seven Members of Congress, GAO determined

--the opinions of experts regarding the perceived impact of the Delaney Clause, which bans the use of cancer-causing food additives, the need to delete or modify it, and alternative ways of doing so;

--the public attitude toward allowing the use of carcinogens in food;

--the social, scientific, and regulatory issues that cause disagreement about the Delaney Clause and the use of food additives that may cause cancer; and

--the regulatory alternatives to the Delaney Clause. (See p. 2.)

WHY THE DELANEY CLAUSE IS AN ISSUE TODAY

The 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act provides that no additive shall be deemed to be safe if it is found to induce cancer when ingested by humans or animals or it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in humans or animals. This provision is known as the Delaney Clause. (See p. 1.)

The Delaney Clause is a source of controversy, an emotional issue, and a target for change.

The heart of the issue centers on Delaney's "zero-risk" concept that no substance, in any amount, may be intentionally added to food if it has been shown to cause cancer.

TOTALLY RELIABLE TESTS TO DETECT AND ASSESS THE RISK OF CANCER FROM FOOD ADDITIVES HAVE NOT YET BEEN DEVELOPED

Tests to determine whether food additives cause cancer and statistical models to assess their risk to humans are available, but they have not yet been developed to the point where many experts totally accept their reliability. The most widely used tests can be divided into four categories:

--Molecular structure analyses provide limited information about the possibility of a substance causing cancer by analyzing its chemical structure. These analyses are not regarded as strong indications of either safety or risk.

--Short-term tests are based on the presumption that cancer is related to changes in cells which can result in mutations. There are now about 100 different such tests, but none can detect every cancer-causing substance.

--Animal tests are generally regarded as the best method available for evaluating a substance's cancer-causing potential. The number, type, location of tumors, and, in some cases, the time it takes for a tumor to develop in test animals and in control animals are compared.

--Epidemiological studies (for example, a comparison of cancer incidence between asbestos workers and other groups) are the most convincing evidence of a substance's human cancer-causing potential. Epidemiological studies can rarely provide useful and timely answers to regulatory problems because of their general insensitivity for detecting relatively small changes in the rate of occurrence of a disease and their retrospective nature. (See pp. 8 to 16.)

EXPERTS GENERALLY AGREE THE DELANEY CLAUSE SHOULD BE CHANGED BUT DISAGREE ON HOW

GAO conducted 50 interviews with biomedical researchers, industry and consumer group

representatives, and former FDA commissioners and general counsels.

With the exception of some consumer group representatives, most experts believed the Delaney Clause should be changed but differed significantly on how to change it. Food safety experts agreed that the principle of the Delaney Clause--not adding cancer-causing food additives to the food supply--is desirable in theory, but most believed that the Clause is impractical and should be changed. (See pp. 20 and 21.)

Proponents of change believe that a goal of absolute safety is unrealistic primarily because scientific advances enable one to (1) detect minute amounts of substances in the parts per billion or trillion range and (2) identify carcinogens in the food supply that may not pose a significant risk to human health. (See p. 20.)

In addition, the proponents of change noted that the risks associated with other hazards in the workplace and the environment are regulated with some discretion; all cancer risk is barred only for food and color additives. Some believe that the cancer risk from certain food additives may be outweighed by the benefits derived from the additive's use. (See p. 20.)

Opponents of change argue that the Delaney Clause is the most effective way to deal with food additives that may cause cancer since not enough is known about cancer to allow their use. Some maintain that, because the risk from cancer-causing substances cannot be quantified, a zero-risk standard is a cautious and prudent societal judgment. (See pp. 20 and 21.)

PUBLIC ATTITUDE REGARDING CARCINOGENIC FOOD ADDITIVES

GAO identified 12 public opinion polls conducted over the past 10 years which addressed the question of food safety. These polls showed that the public approves of the general policy of banning cancer-causing food additives. However, the public is opposed to a ban for specific substances like saccharin which have been in use for a number of years and have perceived benefits. (See pp. 33 to 36.)

DIFFERENT REGULATORY POLICIES FOR DIFFERENT USES OF CANCER-CAUSING SUBSTANCES

Cancer-causing substances are regulated differently within FDA and among FDA and other Federal agencies because of differences in social, economic, and health considerations. Under the Federal Food, Drug, and Cosmetic Act, not all substances added to food are regulated as food additives. (See p. 37.)

Federal laws that regulate pesticides, environmental contaminants, consumer products, and hazardous substances in the workplace require that the risk from exposure to carcinogens be balanced against one or more of the following factors: health, social, economic, and environmental benefits; costs to the consumer and industry; and technological feasibility.

Under these laws, cancer-causing substances are regulated no differently from other toxic chemicals. (See ch. 4.)

CONGRESSIONAL OPTIONS FOR REGULATING CANCER-CAUSING FOOD ADDITIVES

Three obvious alternatives are possible: (1) leave the Delaney Clause unchanged, (2) repeal it, or (3) amend it in some way. (See ch. 5.)

If the Clause were deleted from the Food, Drug, and Cosmetic Act, both carcinogenic and noncarcinogenic food additives would be regulated under the general safety clause. Thus, a cancer-causing food additive could be used if there was a reasonable certainty that no harm would come from its proposed use.

Under the third alternative, amending the Clause, three options could be considered: (1) set an acceptable level of risk, (2) compare risks and benefits, and (3) compare the health risk of using a carcinogen with the health risk of not using it.

Under the first option, FDA would determine that the estimated health risk from the use of the substance would be insignificant or within an acceptable level. Many officials at FDA favored

this approach. In considering this option, the Congress needs to be aware that different mathematical models for estimating human risk can produce widely varying results which differ by many orders of magnitude.

Benefits that can be considered under the risk-benefit option include: (1) health benefits--the substance provides an essential nutrient, (2) economic benefits--reduced cost or increased supply, and (3) other benefits, such as increased appeal--improved aesthetic value and utility.

Under the last option, FDA would be required to balance risks and determine whether a ban or other restriction on the use of a carcinogenic food additive would result in a greater health risk than allowing its use.

If the Congress chooses to address these options, it should consider whether to apply them equally to cancer-causing and non-cancer-causing substances.

MATTERS FOR CONSIDERATION BY THE CONGRESS

GAO believes that the Congress should reexamine whether the Delaney Clause is still appropriate because of (1) advances in the ability of analytical detection methods to identify substances at very low levels, (2) uncertainties about the human risk from low levels of carcinogens, and (3) the inflexibility of the current law. (See p. 57.)

AGENCY COMMENTS

The Department of Health and Human Services said that it is considering alternative approaches that could be adopted for regulating carcinogens in the food supply and that GAO's report would be useful in formulating a policy.

The Environmental Protection Agency concurred with the general findings and conclusions of this report and added that the findings provide a sound basis for GAO's recommendation that the Congress reexamine the Delaney Clause. The Department of Labor and the Consumer Product Safety Commission provided comments which they believed clarified information in the report. (See p. 58.)

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ABBREVIATIONS

CAST	Council for Agricultural Science and Technology
CPSC	Consumer Product Safety Commission
DNA	Deoxyribonucleic Acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
FSC	Food Safety Council
GAO	General Accounting Office
GRAS	generally recognized as safe
NAS	National Academy of Sciences
NCI	National Cancer Institute
OSHA	Occupational Safety and Health Administration
TSCA	Toxic Substances Control Act

CHAPTER 1

INTRODUCTION

> "No additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animals, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal."

This statement, known as the Delaney Clause, was added to the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) (FD&C Act) by the 1958 Food Additives Amendment because of safety concerns about the increasing number of chemicals added to food. The Delaney Clause, which is administered by the Food and Drug Administration (FDA) of the Department of Health and Human Services, stipulates that no substance, in any amount, may be intentionally added to food if it has been shown to cause cancer.

The Secretary of Health, Education, and Welfare 1/ testified in 1960 that:

> "We have no basis for asking Congress to give us discretion to establish a safe tolerance for a substance which definitely has been shown to produce cancer when added to the diet of test animals. We simply have no basis on which such discretion could be exercised because no one can tell us with any assurance at all how to establish a safe dose of any cancer-producing substance.
>
> "Unless and until cancer research makes a breakthrough at this point, the principle in the anti-cancer clause is sound."

However, recent disputes about the safety of saccharin and nitrite have raised questions about the continued appropriateness of the Delaney Clause's "zero-risk" philosophy. These questions generally address the issues of the adequacy of cancer tests and the appropriateness of banning a substance regardless of its value or the degree of risk involved.

1/On May 4, 1980, the Department of Health, Education, and Welfare became the Department of Education and the Department of Health and Human Services. Responsibility for activities discussed in this report was given to the Department of Health and Human Services.

WHY THE REVIEW WAS MADE

Representatives C. E. Grassley, W. C. Wampler, T. Hagedorn, J. G. Martin, R. Nolan, C. Whitley, and I. Skelton asked us to report on issues related to the Delaney Clause and alternatives to regulating carcinogenic food additives. Our work was aimed at determining

--the opinions of experts regarding the perceived impact of the Delaney Clause, the need to delete or modify that Clause, and alternative ways of doing so;

--the public's attitude toward allowing the use of carcinogens in food;

--the social, scientific, and regulatory issues that cause disagreement about the Delaney Clause and the use of food additives that may cause cancer; and

--the alternatives to the Delaney Clause for making decisions about the use of food additives that may cause cancer.

Additional information on our objectives, scope, and methodology is included in chapter 6.

CHANGING HEALTH ISSUES

Since the early 1900s there has been a decrease in acute infectious diseases and an increase in chronic diseases with long latency periods. According to a National Academy of Sciences (NAS) report, in 1900, when life expectancy at birth was 47 years, pneumonia and influenza were the leading causes of death, followed by tuberculosis and combined diarrhea and enteritis. Together these accounted for 550 deaths per 100,000 population, or about 30 percent of total mortality. Heart disease was fourth, killing 137 people annually per 100,000 population, and cerebrovascular disease was fifth. Cancer was eighth, accounting for 64 deaths per 100,000. In 1976, with life expectancy exceeding 70 years, heart disease and cancer were the first and second leading causes of death, respectively. Heart disease accounted for 337 deaths per 100,000 population, cancer accounted for 176, and cerebrovascular disease 88. These three categories of diseases accounted for 68 percent of total deaths; pneumonia and influenza accounted for only 3 percent.

HISTORY OF FOOD SAFETY REGULATION

Innovations in the food processing industry since the early 1900s have resulted in changes in the concerns about the safety of the food we eat. Technology has transformed the food supply from the relatively simple product of local farming and home

preparation into the output of a multibillion-dollar industry. Processing has helped to make foods cheaper, more readily available, convenient, attractive, and generally free from contamination.

The first Food and Drug Act in 1906 reflected the concern for potential harm from unwholesome, impure, adulterated, and misbranded foods. The act provided that food would be considered adulterated if it contained any added poisonous or other deleterious ingredients which would make the food injurious to health. Other provisions related largely to deceptive labeling, insanitation, and use of diseased animals for food. In the 1940s and 1950s, the Congress became concerned about the increasing use of chemicals in the food supply and the lack of knowledge about their long-term health effects on humans. A 1952 congressional committee report recommended legislation to require premarket safety testing for chemical food additives. In 1958 the Food Additives Amendment was added to the FD&C Act. This amendment included the Delaney Clause, which prohibits the approval of cancer-causing food additives. Similar clauses were passed in 1960 and 1962 prohibiting the use of cancer-causing color additives and animal drugs.

In the late 1960s and 1970s, the absoluteness of the Delaney Clause was questioned because of (1) the increasing ability to detect extremely minute quantities of chemicals in foods coupled with uncertainties about the significance of such low levels, (2) concerns about the accuracy and reliability of tests to determine carcinogenicity and the risk to humans, and (3) the possibility that benefits derived from the use of carcinogens could outweigh associated risks.

FOOD ADDITIVE USAGE

The average American consumes yearly about 139 pounds of food additives, color additives, and substances that are generally recognized as safe (GRAS). One of the food safety experts we interviewed during our review (see p. 21) estimated that in 1981 sugar accounted for 80 percent of this total (or about 109 pounds) and salt accounted for 10 percent (or about 14 pounds). Preservatives, artificial colors, and flavors accounted for just over 1 percent (or about 1-1/2 pounds).

Additives are used to prevent or delay spoilage, improve the nutritive value of food, enhance taste, improve texture, provide color to make food more attractive, reduce cost by eliminating certain processing requirements (such as freezing or by extending usable life), retain moisture, increase volume, and more. There are about 2,700 food additives and 33 color additives used in food regulated by FDA. In addition, thousands of indirect additives, such as adhesives used in packaging materials, which may migrate into the food are similarly regulated. Of the types of substances

to which we can be exposed, food additives are special in that they are found in almost all food products and individuals cannot easily control their exposure to them.

REGULATION OF FOOD ADDITIVES

FDA establishes regulations prescribing the conditions under which a food additive may be safely used. The FD&C Act defines a food additive as any substance the intended use of which results or may reasonably be expected to result directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food. Before a regulation can be established, the additive must be shown to be safe and functional for its intended uses (i.e., it must accomplish the effect for which it is to be used--preservatives must preserve).

The 1958 amendment requires that sponsors prove that the proposed use of a food additive will be safe. Petitions filed by them must contain:

--The name and all pertinent information concerning the food additive, including where available, its chemical identity, and its composition.

--A statement of the conditions of the additive's proposed use, including all directions, recommendations, and suggestions for its proposed use, and specimens of its proposed labeling.

--All relevant data on the physical or other technical effects of the additive and the quantity of the additive required to produce such effect.

--A description of practicable methods for determining the quantity of the additive in or on food and any substance formed in or on food because of its use.

--Full reports of investigations made about the additive's safety, including full information on the methods and controls used in the investigations.

In determining the safety of a food additive, FDA considers:

--The probable consumption of the additive and of any substance formed in or on food through use of the additive.

--The cumulative effect of the additive in the diet of humans or animals, taking into account any chemically or pharmacologically related substance or substances in the diet.

--Safety factors generally recognized by qualified experts as appropriate for the use of animal experimentation data.

The concept of safety is not specifically defined by the FD&C Act. The act's legislative history indicates that the Congress intended safety to mean proof of reasonable certainty that no harm will result from the proposed use of the additive, and the regulations implementing the Food Additives Amendment adopt that standard. The Delaney Clause, however, establishes a different safety standard for carcinogens. Once a substance is found to be a carcinogen, no food additive petition for its use may be approved. Any approved food additive found to be a carcinogen must be banned.

Some categories of substances in or added to food are not included in the definition of food additives. These categories are:

--Pesticides or chemicals in or on raw agricultural commodities.

--A pesticide chemical to the extent that it is intended for use or is used in the production, storage, or transportation of any raw agricultural commodity.

--A color additive.

--A new animal drug.

--A GRAS or prior sanctioned substance.

In addition, natural constituents and unavoidable contaminants of foods are not regulated as food additives. Natural constituents are chemicals which normally make up the foods we eat. Unavoidable contaminants are substances which either are required in the production of food or cannot be avoided through good manufacturing practices. Substances in these categories as well as pesticides found in raw agricultural products and processed foods are regulated under different standards than are food additives.

Although color additives and new animal drugs are exempt from food additive status, the FD&C Act sets out standards essentially identical to the Delaney Clause for both. Chapter 4 discusses the above substances and how they are regulated.

CANCER: DEFINITION, CAUSES, AND INCIDENCE

Cancer is defined as the unrestrained, abnormal growth of cells. Cancerous cells push normal cells out of the way, spread, and often migrate to other parts of the body. Cancer is not a single disease but rather a group of diseases occurring in humans and animals. Each type has its own rate of occurrence and often tends to affect certain population groups sharing particular characteristics.

Sex, race, and other hereditary factors, as well as geography, age, and occupation, affect the incidence of cancer. Although cancer can develop quickly, as in some forms of leukemia, for many forms of cancer years may pass between the causal exposure or other event which initiated the process and the discovery that cancer exists.

Although more research is needed, it appears that at times some identifiable cause is responsible for changing the behavior of cells and stimulating their growth. While a single cancer-inducing event can trigger this response, cancer can also be caused by repeated low-dose exposures to some substance or event. Certain risk factors have been identified as potential contributors to cancer development. These factors include cigarette smoking, alcohol, certain dietary patterns, radiation, sunlight, occupational hazards, water and air pollutants, heredity, and predisposing medical conditions.

CHAPTER 2

TESTS TO DETERMINE WHETHER SUBSTANCES CAUSE CANCER AND METHODS USED TO ESTIMATE THE DEGREE OF HUMAN RISK OFFER NO EASY ANSWERS

Tests to determine whether food additives cause cancer and statistical models to assess their risk to humans are available, but they have not yet been developed to the point where many experts totally accept their reliability. Several types of studies or analyses are used as indicators of a substance's cancer-causing capability. (See app. II.) The most widely used tests to assess carcinogenicity are:

--Molecular structure analyses, which compare the structure of a substance with known carcinogens and noncarcinogens. These analyses provide limited information about the possibility of a substance causing cancer and are used primarily as screening devices for potential carcinogens.

--Short-term tests, which are based on the presumption that cancer is related to changes in cells which can result in mutations. 1/ Presently these tests are used primarily as screening devices for potential carcinogens.

--Long-term bioassays in laboratory animals, which are fed high doses of chemicals for approximate lifetimes (often several years) to determine whether a substance is likely to cause cancer. Human risk is usually estimated or extrapolated from animal study results.

--Epidemiological studies, which associate cancer in human populations to exposure to a specific substance. By their nature, however, these studies are retrospective since it is unethical to expose humans to potentially cancer-causing substances. 2/

1/Mutagens ("mutagenic substances") produce a permanent, transmissible change in the genetic material (deoxyribonucleic acid, or DNA) of a cell.

2/Epidemiology is a science that deals with the incidence and distribution of disease in a given population. Epidemiological studies compare the incidence of a disease, for example bladder cancer, in a population exposed to a particular chemical to the incidence of the disease in an unexposed population in order to identify causes for the disease. The two populations should be closely matched according to such factors as age, sex, and smoking habits.

The following material summarizes information we obtained from our interviews with food safety experts (see ch. 3) and from publications we reviewed (see app. III).

MOLECULAR STRUCTURE ANALYSES PRODUCE LIMITED INFORMATION ON CANCER-CAUSING SUBSTANCES

Most cancer experts believe that, although chemical structure analysis can be helpful, it provides limited information on substances that may cause cancer. 1/ Groups of closely related chemicals may differ with respect to carcinogenicity. For example, the substance 2-acetylaminoflourene is a well-known carcinogen, while its close chemical relative 4-acetylaminoflourene has not been shown to be a carcinogen.

Experts we interviewed unanimously agreed that chemical similarity should not be used to determine carcinogenicity but should be used in making decisions about which chemicals are or are not suspect and which should be further tested. These analyses are inexpensive and can be completed in a matter of days.

SHORT-TERM TESTS MAY BE USEFUL TO SHOW CARCINOGENICITY

Over 100 short-term tests have been developed to provide fast and inexpensive answers to determine if a substance is a mutagen. These short-term mutagenicity tests are based on the presumption that cancer is related to changes in cells which can result in mutations or changes in the DNA. The major factor influencing the acceptance or rejection of a short-term test as a method for identifying carcinogens is evidence that the test can distinguish between carcinogens and noncarcinogens. No short-term test can detect every cancer-causing substance. 2/

Short-term tests are popular because:

--It is impractical to use long-term tests to determine if the many thousands of environmental and industrial chemicals are carcinogenic. Four million known chemicals exist, of which about 60,000 are in widespread use. About 1,000 new chemicals enter the environment each year.

1/See Occupational Safety and Health Administration Regulation Covering the Identification, Classification, and Regulation of Potential Carcinogens (45 FR 5174-77, Jan. 22, 1980).

2/Office of Technology Assessment, "Assessment of Technologies for Determining Cancer Risks From the Environment," June 1981, p. 120.

--They usually can be completed in days or weeks as compared to years for animal tests.

--They are inexpensive, with costs varying from $100 to several thousand dollars, whereas long-term tests may cost from $400,000 to $1,000,000.

--Evidence exists to indicate that most chemical carcinogens are mutagens and that many mutagens are carcinogens.

--There are an increasing number of examples where short-term tests have accurately predicted the carcinogenic potential of chemicals.

The Ames test

Of the 100 short-term tests, the "Ames test" is the best studied and most widely used. Basically, the Ames test involves mixing the chemical under test with a bacterial culture and then manipulating the culture so that only mutated bacteria will grow. In some studies the Ames test has shown that 90 percent of the examined animal carcinogens were mutagenic and that 88 percent of the examined chemicals classified as noncarcinogens were not mutagenic. Researchers have agreed that the Ames test shows that there is a correlation between mutagenicity and carcinogenicity, but there is some disagreement on how frequently carcinogens are correctly identified--70, 80, or 90 percent of the time.

Usefulness of short-term tests

The overwhelming majority of experts we interviewed believed that short-term test results presently do not, in the absence of data from long-term tests (animal bioassays and epidemiology), constitute definitive evidence that a substance does (or does not) pose a hazard to humans. Positive results from short-term tests, however, supplement results from other tests and are considered suggestive evidence of carcinogenicity. Carcinogens that are not detected (false negatives) and the noncarcinogens that are falsely detected (false positives) constitute the problems with test results. Most scientists have recommended using a battery of short-term tests to detect substances that cause cancer in animals because no single short-term test can detect every carcinogen. However, no generally accepted group of tests exist.

Industry scientists agreed that short-term tests can provide an early warning that a substance is likely to be a carcinogen. A positive result usually means that a new substance will not be further tested and that it will not be commercially produced. It is not that industry scientists believe short-term tests are infallible; rather, they believe that the investment of additional time, effort, and money in a chemical that is apt to be a potential carcinogen is a poor business decision.

RESULTS FROM ANIMAL TESTS GENERALLY ACCEPTED, BUT DESIGN AND DATA INTERPRETATION QUESTIONED BY SOME EXPERTS

Animal studies are generally regarded as the best method available for evaluating a substance's cancer-causing potential. 1/ Most substances which have been proven carcinogenic by direct observation in humans have also been shown to be carcinogenic in experimental animals. However, the high doses of substances to which animals are exposed and the interpretation of test results have been questioned by many industry scientists we interviewed. They also mentioned that animal studies are costly and take several years to complete.

Identification of carcinogens through animal tests

Long-term animal tests are conducted over several years, during which time test animals are fed high dose levels of a chemical substance. Mice and rats are most often used for long-term animal tests because they are small, thereby requiring less space, have short lifetimes (2 to 3 years); and are cheap to feed, buy, and house. In addition, a large amount of information exists about their genetics, breeding, housing, and health.

Test animals are compared to a control group, which is not exposed to the substance. Scientists compare the number, type, and location of tumors and, in some cases, the time it takes for a tumor to develop in the test animals and in the control animals. Statistical techniques are used to evaluate the results and determine, after careful evaluation of all relevant factors (see p. 14), if the substance under test can cause cancer.

Many cancer studies follow the National Cancer Institute (NCI) guidelines for long-term animal tests which specify that:

--Each chemical substance must be tested in both rats and mice.

--About 600 animals are necessary for each test.

--Animal exposure to a chemical substance is to begin at 6 weeks of age and continue throughout the animal's lifespan.

1/Office of Technology Assessment, "Cancer Testing Technology and Saccharin," Oct. 1977, p. 11.

--Test animals are to be divided into three groups; one group is not exposed to the chemical substance, another group is given the maximum tolerated dose, 1/ while a third group is given less than the maximum tolerated dose.

--The method of administering the chemical substance to the animal should mimic human exposure. For example, feeding studies should be conducted for chemical substances to be used as food additives.

--Pathological examination 2/ to detect tumors and other toxic manifestations must be executed under the direction of a pathologist.

A long-term animal test may cost more than $500,000 and take up to 3 or 4 years to complete, of which 6 months may be required to determine dose levels with an additional 24 months needed to expose the test animal to the chemical substance. Pathology examination of tissues from the animal and evaluation of the data may take 12 months. Because of practical limitations, such as the high cost of testing and the limited number of laboratory facilities, only a relatively small number of substances can undergo this extensive testing.

Scientists believe that a positive result from an animal test indicates a potential cancer hazard in humans because:

--None of the approximately 140 carcinogens found to cause cancer in rodents have been proven to be noncarcinogenic in humans, and of the approximately 30 known human carcinogens, only 2 are not proven animal carcinogens.

--Most chemicals shown to induce cancer in one mammalian species also induce cancer in other mammalian species when properly tested. Although susceptibility varies from species to species, there are few documented cases of carcinogens which cause tumors in only one species.

--Animal tests have predicted several human carcinogens.

1/Maximum tolerated dose is generally defined as the highest dose that can be given that would not alter the animals' normal lifespan from effects other than cancer.

2/Veterinary pathology is a branch of medicine that studies the essential nature of a disease in animals, especially the structural and functional changes in tissues and organs of a body which cause or are caused by disease.

--Development of tumors in various species of animals, including humans, is similar.

--Animals and humans have basic similarities in the way their cells and tissues respond to carcinogens.

Critics of animal tests argue that:

--Doses of substances to which test animals are exposed (maximum tolerated dose) are too high and are not predictive of the effects of human exposure.

--Some animals used for testing are so biologically different from humans that results from them have little or no value.

--Some animals (or organs of test animals) are extremely sensitive to cancer-causing substances.

--Benign tumors (those that do not metastasize, i.e., spread in test animals) have no value in defining carcinogenicity.

--Interpretation of test data is associated with a mindset that one molecule of a substance associated with cancer must be banned.

Controversy exists over dose levels given to test animals

Seventeen of the nineteen industry scientists who discussed animal tests believed that extremely high chemical doses given to animals during feeding studies may alter metabolism or cause unusual toxic responses and therefore cause cancers that would not be found at lower dose levels.

However, most biomedical researchers, consumer representatives, and former regulators we interviewed agreed with the concept of giving test animals high dose levels. They believed that high dose levels are necessary to (1) guard against a false negative (carcinogens that are not detected) and (2) increase tumor incidence to a level that can be identified in the small number of test animals. They expressed the belief that, as the dose of a substance that causes cancer is increased, the number of exposed animals that develop cancer also increases. To conduct a valid experiment at high dose levels, about 600 animals are required; to conduct a valid experiment at low dose levels, many more animals would be needed.

Are rodents appropriate test animals?

Eight scientists and seven industry representatives questioned the use of rodents as test animals. They noted that differences

exist between humans and rodents in metabolism, excretion, and lifespan and believed these to be valid reasons for questioning results from rodent tests. Also, they pointed out that animal and human diets are quite different.

Some inbred test animals may be extremely sensitive to carcinogens; their organs may also be very sensitive to the point where such sensitivity may invalidate test data. Also, liver tumors are common in some strains of mice, but infrequently found in humans as a primary tumor. Therefore, the meaning of any finding of liver tumors in certain strains of mice may be questionable as it relates to human risk. 1/

The International Agency for Research on Cancer considers mouse liver tumors as "limited evidence" for carcinogenicity and as "indicators of carcinogenicity" if scientific experience and judgment are used in interpreting test data. While some strains of mice commonly selected for testing have a spontaneous development of one or more cancers, studies on mouse liver carcinogens showed that these chemicals often cause cancer in other organs or in other animals. 2/

Some experts believe that FDA's analysis of animal study results may not be impartial

Ten industry scientists said that FDA's qualitative and statistical analysis of animal study results is not impartial. They believed that FDA merely counts tumors without reference to other aspects of data interpretation. They noted that it is questionable whether benign tumors in experimental animals should be taken as evidence that a chemical causes cancer. Both benign and malignant tumors are found in experimental animals. In their assessment of risk, Federal agencies do not distinguish between benign and malignant tumors when they believe that a benign tumor can become malignant. 3/

1/Office of Technology Assessment, "Assessment of Technologies for Determining Cancer Risks From the Environment," June 1981, p. 120.

2/Tomatis, L., Partensky, C., and Montesano, R. "The Predictive Value of Mouse Liver Tumor Induction in Carcinogenicity Testing: A Literature Survey," International Journal of Cancer, 12:1-20, 1973.

3/Office of Technology Assessment, "Assessment of Technologies for Determining Cancer Risks From the Environment," June 1981, p. 127.

FDA and NCI scientists stated that their evaluation of animal studies does not involve a mere tumor count. Although a statistically significant increase in tumors at a tissue site is important in determining whether a substance causes cancer, NCI and FDA also consider other factors in assessing test results. These factors include, according to scientists we interviewed, expert knowledge of laboratory animal disease and the chemical reactivity of the test substance, compliance with test guidelines, and many direct and indirect observations which combine with general knowledge of the phenomena under study.

In 1978 FDA established, within its Bureau of Foods, a Cancer Assessment Committee to review cancer data. The committee reviews all experimental evidence, evaluates its significance, and takes appropriate action to resolve outstanding scientific problems and when possible determines the carcinogenic status of the substance under study. If the committee is unable to resolve outstanding scientific issues, it may recommend formation of an interagency working group composed of eminent Government scientists to evaluate the experiment's scientific merit. Since the committee was formed in 1978, it has reviewed 26 food and color additives, of which 9 were determined to be carcinogenic.

EPIDEMIOLOGICAL STUDIES CANNOT PROVIDE TIMELY ANSWERS

Positive results from human epidemiological studies (for example, a comparison of cancer incidence between asbestos workers and other groups) are the most convincing evidence of a substance's human cancer-causing potential. 1/ By their nature, however, these studies are retrospective since it is not ethically acceptable to intentionally expose people to a potentially cancer-causing substance. Because it is generally believed that cancer takes a long time to develop, exposure to a cancer-causing substance will usually not show any immediate results. Epidemiological studies can rarely provide timely answers to regulatory problems. Such studies take years to perform.

Epidemiological studies consider human experience

The science of epidemiology seeks to determine the distribution and causes of diseases and injury in humans. It focuses on groups rather than individuals. Epidemiological studies attempt to answer two questions:

1/National Academy of Sciences, Committee for a Study on Saccharin and Food Safety Policy, "Food Safety Policy: Scientific and Societal Considerations," March 1979, p. 5-5.

--Is there a positive association between a particular exposure and the occurrence of disease in humans?

--If there is, is it causal?

Experts advised us that, where valid epidemiological data exist, such data provide the best evidence to support an association between exposure to a substance and the development of a human disease. Human epdiemiological data can be used to directly estimate human risk.

There are several types of epidemiological studies. Each provides different types of information. Cohort studies identify groups of healthy individuals with known exposure or lack of exposure to particular food substances, for example, and follow these individuals to determine the incidence of a suspect food-induced disease. Case-control studies identify individuals with the suspect disease and seek to determine their prior consumption of the potentially harmful food substance. Both kinds of studies require control groups that differ as little as possible from the exposed or diseased persons except for the particular variable being tested (exposure to the chemical). Establishing suitable controls is one of the more difficult tasks of epidemiology.

Limitation of epidemiological studies

NAS reported that correlating food consumption with cancer, a disease associated with a long latency period and long exposure time, is difficult. 1/ Most cancers have a latency period of at least 5 to 10 years; as much as 40 to 50 years may elapse between exposure and evidence of cancer. Retrospective studies are difficult to conduct because they require large populations, adequate exposure analysis, control groups, accurate records, and careful analysis of confounding factors. 2/ Epidemilogical studies are generally insensitive and are usually incapable of determining cancer risks unless they are quite large or represent a discrete population. They are also very expensive and time consuming. A study may take 3 or 4 years to complete and cost over $2 million.

1/National Academy of Sciences, Committee for a Study on Saccharin and Food Safety Policy, "Food Safety Policy: Scientific and Societal Considerations," March 1979, p. 5-12.

2/A confounding factor is a factor that contributes to a disease incidence. For example, it might be concluded that an inexpensive food item is a risk factor for a disease. However, if that food were eaten primarily by poorer people, then a condition associated with poverty might contribute to the disease incidence. Such a condition would be a confounding factor in the study because the disease actually would be entirely or partly due to the condition rather than to the food item itself.

Problems in interpreting and using epidemiological studies

Epidemiological studies can rarely provide timely answers to regulatory problems. In a regulatory design to prevent cancer in humans such as the Delaney Clause, the time required to generate epidemiological data would preclude their use in initial regulatory decisions.

Epidemiological methods are also generally insensitive for detecting relatively small changes in the rates of occurrence of a disease. Because of this insensitivity, a negative finding in a well-conducted study does not rule out the possibility that a serious hazard might exist. Even positive findings may not demonstrate that an excessive incidence of cancer is caused by a single substance because (1) people are exposed to many substances, (2) methods of estimating exposure levels, especially for foods, are poor, and (3) confounding factors, such as occupational exposure and smoking, may be present.

HUMAN RISK ASSESSMENT-- A DIFFICULT PROCESS

Risk assessment is a controversial and complicated procedure aimed at determining the relationship between the incidence of cancer in animals and the potential for cancer in humans. About 64 percent of the experts (who expressed an opinion) we interviewed believed that risk assessment, though difficult, has to be done to allow for a realistic food safety system. The other 36 percent believed that risk assessment was a difficult task given the present state of knowledge.

Risk assessment assumes that a chemical substance associated with an increased cancer incidence in animal bioassays is likely to be a human carcinogen. Extrapolation to humans of cancer incidence in animals is necessary to quantify the expected degree of risk for humans exposed to concentrations of chemicals that differ from those given to animals in laboratory tests. Two steps are involved in this procedure:

--Extrapolating the results of high doses of the test substance in animals to low doses of the test substance in animals (corresponding to human exposure), which requires using one of several mathematical models.

--Extrapolating from the estimated low dose animal risk to human risk at similar doses.

Extrapolating from high doses to low doses

Animal studies use higher levels of chemical substances than are commonly found in human exposure. Extrapolation from high to low dose requires the use of some mathematical model which relates the dose level of a particular chemical substance to an observable response--that is, the occurrence of a particular type of tumor at any time within the animal's natural lifespan.

The choice of mathematical models is crucial to the outcome of low dose extrapolation. Most models generally assume the absence of a threshold for a carcinogen. That is, no matter how minute the exposure to a cancer-causing substance, some risk of contracting cancer exists. Scientists generally agree that, even if thresholds do exist, the methods for determining them are not presently available.

Different models produce results which may differ by many orders of magnitude at low-dose levels. The variations involved in extrapolating from high-dose animal experiments to low-dose risk to humans may be illustrated by the NAS report 1/ on saccharin, which cited 10 mathematical models for extrapolating animal data to human risk. This report showed that the highest estimated risk per million people exposed over a lifetime was more than 5 million times greater than the lowest estimated risk. All estimates were derived from the same set of experimental data on rats. The report concluded that, if all 220 million Americans alive today consumed one bottle of diet soft drink per day for the rest of their lives, between 0.22 and 1,144,000 cases of bladder cancer could result over the next 70 to 80 years.

Several theories on the nature of carcinogenesis serve as the basis for different low-dose extrapolation models. Most Federal regulatory agencies use the "single-hit" theory. This assumes that (1) tumors result from some random event or "hit" which produces an irreversible change in the cell's DNA, (2) the probability of this event, or "hit," attributable to the carcinogen in question, is proportional to the exposure level, and (3) no threshold exists for a carcinogen. The one-hit models are conservative in that they usually associate the highest risk with a given dose.

Other models predict that a threshold dose exists below which a carcinogen has no effect. However, because the mechanisms which produce cancer are so little known or understood, scientists have been unable to determine whether a threshold exists.

1/National Academy of Sciences, "Saccharin: Technical Assessment of Risks and Benefits," Report No. 1, November 1978, p. 3-72.

Animal to human carcinogenicity correlations are rough estimates

Despite uncertainties, the only available method for quantifying human risk is to extrapolate from animal data. Enough is known to provide rough predictions for cancer rates in the human population.

Animal carcinogens are generally assumed to be human carcinogens. Test animals, usually rodents, differ from humans in size, weight, metabolism, and biochemistry. Exposure to a food additive may be adjusted on the basis of the relative sizes of the test animal and humans or on their relative body weights.

However, animals are exposed to test substances in a carefully controlled environment, whereas humans are exposed to many possible carcinogens in an uncontrolled environment. Effects of one substance on animals may be very different from effects of the same substance on humans. Additive, synergistic, 1/ and antagonistic 2/ interactions among other carcinogens can produce results in the human population which may not be seen in laboratory animals.

Other factors in assessing human risk

Two other factors in assessing human risk are exposure to and potency of a chemical substance. That is, exposure of a few people to a weak carcinogen would be less of a public health hazard than exposure of many people to a very potent carcinogen.

Specific groups within the population may be at higher risk than the rest of the population. These groups may include infants, children, and pregnant women. A population may be exposed frequently or infrequently, over many years or within a short period. According to food safety experts all of these characteristics are relevant in quantifying human risk.

Potency, or strength, of a carcinogen is an important element of any risk estimate. Experts we interviewed agreed that the potency of chemical carcinogens varies greatly. This variation could result in large differences when estimating human risk--perhaps by a factor of 100,000 or 10 million. Experts we interviewed also agreed that chemical carcinogens could presently be ranked only in the order of their relative potency--that is, aflatoxin, one of the

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1/Two or more substances interact producing more cancer than can be accounted for by adding the effects of each.

2/Two or more substances interact producing less cancer than the total each would produce individually.

most potent carcinogens in animals, is much stronger than saccharin, one of the weakest animal carcinogens.

CONCLUSIONS

There are no simple solutions to determine whether a substance causes cancer. Each step in food additive testing--molecular structure analysis, short-term tests, and animal bioassays--involves uncertainties. A separate task, risk assessment, requires extrapolation from laboratory animal data to human risk. The choice of animal tests, biological assumptions, and mathematical models can have a significant impact upon determining and estimating human risk. The estimated number of human cancer cases can vary widely. Science does not always yield a single, incontrovertible answer. What causes cancer and how much of a substance is needed to initiate a carcinogenic reaction remain unknown. The expansion of scientific knowledge to allow researchers to determine whether there is a safe level of a carcinogen remains a challenge for the future.

CHAPTER 3

REGULATING CANCER-CAUSING FOOD ADDITIVES--

A CONTROVERSIAL ISSUE

The Delaney Clause requires FDA to ban all food additives shown to cause cancer. This "inflexible" statement of policy has become the center of controversy. Food safety experts we interviewed agreed that the principle of the Delaney Clause--not adding cancer-causing food additives to the food supply--is desirable in theory, but most felt that the Clause is impractical and should be changed. However, their suggestions for legislative change varied.

Proponents of change believe that a goal of absolute safety is unrealistic because scientific advances enable one to (1) detect minute amounts of substances in the parts per billion or trillion range and (2) identify carcinogens in the food supply that may not pose a significant risk to human health. They believe that the Delaney Clause is inconsistent with other requirements of the FD&C Act since more stringent standards are applied to food additives than to natural constituents and contaminants in food. For example, aflatoxins--potent cancer-causing substances which occur in corn and peanuts--are not subject to the Delaney Clause and are permitted at low levels in the food supply. (See ch. 4.)

In addition, the proponents of change noted that, while the risks associated with other hazards in the workplace and environment are regulated with some discretion, all cancer risk is barred only for food and color additives. Some believe that the cancer risk from certain food additives may be outweighed by the benefits derived from the additives' use. Still others question the usefulness of animal studies and the various methods of extrapolation.

Those favoring change believe that the Delaney Clause has hampered the development of new food additives. In addition, they stated that other Federal regulatory agencies, including the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Consumer Product Safety Commission (CPSC), have been affected by the Delaney Clause because it was the forerunner of these other agencies' legislation and their actions reflect an attempt to establish zero exposure goals.

Opponents of change argue that the Delaney Clause is the most effective way to deal with food additives that may cause cancer since not enough is known about cancer to allow their use. Those opposing change note that the regulation of food is different from the regulation of other substances, such as pesticides or industrial chemicals, since a person cannot live without food. Some

maintain that, since risk from cancer-causing substances cannot be quantified, a zero-risk standard is a cautious and prudent societal judgment.

Similarly, public opinion polls reveal ambivalent and contradictory attitudes by those polled. The public's, as well as food safety experts' suggestions for changes in the law have resulted in a wide variety of views.

We interviewed four groups of experts, using a questionnaire, to discuss Delaney Clause issues. (See app. I for a list of experts and their affiliations.) We interviewed 9 former FDA regulators, including 5 former Commissioners and 4 former General Counsels; 12 biomedical researchers; and representatives from 3 biomedical research organizations, 6 consumer groups, 15 food and chemical companies, and 5 trade associations. Because we could not define the universe of experts, no statistically valid projections can be made from our data. However, the individuals interviewed were recognized as food safety experts by most of the Federal and private officials that we contacted. (See p. 61.)

EXPERTS AGREE ON THE NEED FOR CHANGING THE DELANEY CLAUSE

When the Congress enacted the Delaney Clause in 1958, there were about 1,000 direct additives in the food supply. Many of those substances had not been tested for carcinogenicity. The Congress believed, at that time, that some of the additives might pose problems and that these few could be eliminated from the food supply with little difficulty. Since that time, advances in carcinogenesis testing and analytical capability have established that more and more substances, including many useful and some apparently essential ones, may cause cancer. An overwhelming majority (80 percent) of food safety experts we interviewed favored changing the Delaney Clause, as shown on the next page.

Attitudes Toward
Amending the Delaney Clause (note a)

	Amend Delaney Clause	Leave Delaney Clause unchanged
Former FDA Commissioners and General Counsels	8	1
Biomedical researchers	12	3
Consumer group representatives	-	b/6
Food and chemical companies and trade associations	20	-
	40	10

a/The views and responses contained in this table and the other tables throughout this chapter do not necessarily equal the total number of experts interviewed because some experts did not respond to certain questions and some provided more than one answer to a particular question. In addition, because of experts' time constraints, we could not complete some interviews.

b/One consumer group representative proposed extending the Delaney Clause concept to include mutagenicity (transmissible changes to offspring) and teratogenicity (birth defects not transmissible to offspring).

Former regulators said that:

--The Delaney Clause is redundant; other sections of the FD&C Act provide ample authority for regulation of carcinogenic substances.

--The Clause is too confining because of its inflexibility; it leaves no room for scientific evidence that an animal carcinogen may not be an actual risk to humans.

--A zero level of risk for food additives is unrealistic and unreachable; some modified form of socially acceptable risk is required.

--The Clause prevents exercise of good judgment. The Congress should abolish it. The safety provisions are already there, and FDA seldom uses the Clause anyway.

Biomedical researchers commented that:

--The Delaney Clause is a major problem when food additives have to be removed from the market because of the social and economic pressures which result.

--The Clause is a political, not a scientific issue.

--In the real world, zero risk does not exist. There may be no advantage in retaining the Clause if it requires reaching for a zero risk.

--Public health policy has to be based on protecting the most susceptible individuals, which the Clause tends to do. For food additives, retaining the absolutism of the Clause is preferable to a change in the law which would open the door to possible risks.

--The Clause is not harmful at the moment, and we need a good deal more sophistication in testing procedures before we can even worry about taking the trouble to start over.

--It would be disastrous for FDA to be given flexibility to make decisions because it would be in the midst of every scientific, political, social, and economic battle. It would be a public health, public regulatory nightmare if FDA has flexibility.

Consumer group representatives defended the Delaney Clause, noting that:

--Science has not advanced enough to change the zero tolerance. We don't know. We can't extrapolate from animal data to human risk.

--There is no justification for changing the Clause. No carcinogens should be put in the food supply because the magnitude of risk to society cannot be calculated.

--Food additives are not like prescription drugs or chemicals in the workplace. Everybody is exposed to food additives in the general food supply. Whether they want to be or whether they know they are, they cannot avoid it. The fact that a chemical substance is added to the food supply raises special considerations.

Industry representatives strongly argued for changing the Delaney Clause because:

--Zero risk is not realistic; it is an impossible goal.

--The Clause is too inflexible; more scientific judgment is needed.

--The principal concern with the Clause is the flavor of absolutism. It says thou shalt not do something in quite simple language, and by doing this it literally brings science to a standstill. By taking that approach, there is a considerable potential for economic harm by removing useful materials without a corresponding benefit to human health.

--Scientists now recognize that the nonspecificity of cancer assays and the fact that other variables can influence tumor response require expert evaluation. Experts recognize also that all toxicological data that are pertinent to a given substance must be considered in making safety evaluations of substances, and the absolute language of the Clause does not permit this.

--The Clause is overly simplistic. The definition or the borderline as to what was zero when the Clause was enacted versus what is zero now has to be brought into perspective.

EXPERTS DISAGREE ON ALTERNATIVES TO THE DELANEY CLAUSE

Problems have occurred with invoking the Delaney Clause in the saccharin and nitrite cases because of the lack of substitute products. These controversies have led to suggestions that the Clause be amended or deleted. Suggestions for change include:

--Risk-benefit analysis, which involves enumeration of the risks and benefits (which can be health, economic, aesthetic, etc.). A general balancing of risks and benefits is required. (See ch. 5.)

--Risk-risk analysis, which involves comparing the health risk from using the substance with the health risk from not using it. (See ch. 5.)

--Setting a socially acceptable level of risk, which involves determining whether the risk from a particular additive is greater or less than some predetermined socially acceptable level. Use of risk assessment techniques, with their attendant uncertainties, is required. (See ch. 5.)

--Informed consumer choice, which involves product labeling similar to that used for saccharin and cigarettes. This assumes that the consumer can be given adequate information to make a rational decision.

The following table shows the opinions of food safety experts who believe that the above alternatives are feasible or effective.

Food Safety Experts' Opinions of Suggested Alternatives to the Delaney Clause (note a)

	Feasibility of risk-benefit	Feasibility of risk-risk	Feasibility of acceptable level of risk	Effectiveness of labeling
Former FDA Commissioners and General Counsels	3	2	3	2
Biomedical researchers	6	3	7	3
Consumer group representatives	0	3	1	0
Food and chemical companies and trade associations	5	5	13	5
	14	13	24	10

a/See note a, p. 22.

While food safety experts may support the feasibility or effectiveness of a particular alternative, they may not necessarily favor replacing the Delaney Clause with that alternative. For instance, of the 50 interviews we held, 13 experts said that the risk-benefit regulatory approach should be adopted, 4 favored replacing the Clause with risk-risk evaluations, 13 favored establishing an acceptable level of risk, while none endorsed the use of labeling as an alternative to the Clause.

Views on risk-benefit analysis

Some remarks by former FDA regulators on using risk-benefit analysis include:

--Risks and benefits cannot be quantified.

--A useful model for risk-benefit evaluation is not available at this time.

--Consideration of economic factors, rather than risk to human health, is inappropriate.

Biomedical researchers observed:

--For many substances a tradeoff exists but risks should be considered first.

--Risk-benefit is a difficult but necessary process.

--Risk-benefit is fraught with uncertainty.

--Risks and benefits are subjective and not comparable.

Even though none of the consumer group representatives wanted to amend the Delaney Clause, they stated that:

--There is no adequate mechanism for generating data on alleged benefits and weighing them against the risk of cancer.

--Consumers would be asked to take the health risks, while most of the economic benefits might accrue to producers.

--Consideration should be given only to health benefits and not to economic benefits.

--Benefits cannot be proven.

Industry representatives suggested that:

--We must evaluate benefits as well as risks because we will never have a zero-risk situation in the real world.

--Economic impact, if significant, ought to be a part of the equation. Safety is a paramount consideration.

--Although health and safety are overriding considerations, economic factors should no longer be ignored.

--Benefits are too subjective to measure.

Views on acceptable levels of risk

The comments of the former FDA regulators were:

--It's a garbage in/garbage out situation because, if the underlying data are poor, then the mathematical models won't produce reliable results.

--The real virtue of quantitative risk assessment is that it enables you to avoid the all-or-nothing Delaney Clause result, which is probably impracticable for indirect additives.

--It is impractical.

--The one change in the Clause that would seem most logical would be to provide for greater leeway for mild carcinogens on the part of FDA in its regulatory actions.

--The risk levels set and the risks accepted should be formalized.

--An addition should be made to the Clause requiring FDA, before invoking the Clause, to prepare, with the help of experts in cancer causation, a written analysis of the data and an explanation of why it was scientifically sound to conclude that a substance was a carcinogen.

The biomedical researchers noted that:

--An acceptable level of risk of 1 in 100,000 over a lifetime is a very low level of risk. The risk of dying of cancer in a lifetime is 1 in 5.

--More work is needed in this area to make the process feasible.

--We take acceptable risks every day. When you compare the risks of air pollution and automobiles, the risks of food additives are probably miniscule.

Consumer group representatives argued that:

--Acceptable risk seems reasonable provided it is abstract. When it becomes very personal, it becomes very unacceptable.

--If each food additive has a risk level of 1 in 1 million, your dinner may have 5 additives; this raises the risk from dinner to 5 in 1 million.

--It is the wrong direction to go to add new chemicals into society based on an assumption of acceptable level of risk. We may have to accept some level of risk for existing chemicals.

--The numbers used are frightening because chemicals that would kill tens of thousands of people would be accepted.

Food industry representatives observed that:

--The problem is to define such a level of acceptable risk and then get public acceptance.

--Each substance should have its own risk level, depending on such things as exposure level and usage.

--Society is probably willing to risk 1 death per million population per year.

--A specific level is too confining; a range of risk should be used.

Views on labeling

A consensus emerged among food safety experts we interviewed. They asserted that labeling was ineffective; labels are not often read by consumers, and labels should be used as a supplementary tool especially for the benefit of high-risk groups (i.e., the elderly, pregnant women).

IMPACT OF THE DELANEY CLAUSE ON FOOD ADDITIVES

While the Delaney Clause has been used to ban only two minor indirect additives (see p. 41), its impact extends beyond its limited use. Manufacturers stated that, if a food additive under test showed signs of possible carcinogenicity, they would stop further development because the Clause would preclude FDA approval. In addition, they said that the cost of testing (over $500,000 for an animal bioassay) discourages development of suspected cancer-causing food additives. Industry representatives perceived a serious threat from the Delaney Clause because they thought it has been invoked more frequently than it has been. Industry representatives said that FDA used the Clause to ban Red Dye No. 2 and cyclamates, yet action on these substances was taken under other statutory authority.

Twenty-six experts stated that the Delaney Clause has hampered innovation and the development of new food additives by manufacturers. Industry representatives noted that FDA has approved very few food additives in the past 10 years. However, the Director of the Bureau of Foods' Division of Food and Color Additives stated that, while the Delaney Clause may have hindered the development of some food additives, overall he attributed the decline in the number of food and color additive petitions submitted to FDA to (1) testing expenses for manufacturers and (2) the availability of alternative products. The Director added

that the number of food additive petitions submitted to FDA declined from 111 in 1970 to 44 in 1979. Of these, 75 were approved in 1970 while 17 were approved in 1979.

Although industry representatives believed the Delaney Clause has hindered the development of new food additives and new uses of food additives, other experts we interviewed did not agree, as shown below.

Impact of the Delaney Clause on Food Additives (note a)

	The Delaney Clause inhibited development of new additives			The Delaney Clause inhibited development of new uses of approved additives		
	Yes	No	No response (note b)	Yes	No	No response (note b)
Former FDA Commissioners and General Counsels	2	4	3	2	2	5
Biomedical researchers	7	2	6	5	-	10
Consumer group representatives	2	4	-	3	1	2
Food and chemical companies and trade associations	15	3	3	8	2	11
	26	13	12	18	5	28

a/See note a, p. 22.

b/This column includes food safety experts who did not respond to or had no basis to make a judgment on the issue.

Views on developing new food additives

Former FDA regulators declared that:

--The Delaney Clause has rarely been used; the only two substances banned were minor indirect additives.

--The development of short-term tests has increased the intimidating effect of the Clause because all compounds are screened for toxicity during development.

Biomedical researchers reported that:

--The high cost of testing discourages both the development of new food additives and of new uses for approved additives.

--Use of maximum tolerated dose in animal tests has discouraged development because such tests often show carcinogenicity.

Consumer group representatives observed:

--No potentially useful direct food additive has been kept from the public because of the Delaney Clause.

--If the development of a food additive under test has been ended because of the Clause, this is desirable because it has kept a cancer-causing substance from the marketplace.

Industry representatives had a different analysis of the present regulatory situation:

--Very few food additives have been approved in the last 10 years.

--The high cost of testing inhibits innovation.

--A chemical has a 30- to 50-percent chance of being found carcinogenic when tested at maximum tolerated dose. Since a finding of carcinogenicity (a positive test result) cannot be overturned by one or more failures to find carcinogenicity (a negative test result), there is a reluctance to test previously approved food additives for new uses.

IMPACT OF THE DELANEY CLAUSE ON FEDERAL AGENCIES

Public debate over food additives has intensified since the recognition in 1977 that saccharin, the only artificial sweetener approved for use at that time, was a weak carcinogen. That episode was followed by the controversy over the possible carcinogenicity of nitrites. Attention has focused primarily on the Delaney Clause in connection with food and color additives. One question which emerged following these episodes was whether FDA has been placed in an impossible regulatory dilemma because of the alleged inflexibility of the Clause. In both instances an irreplaceable, widely used substance was to be removed from use.

There are two arguments concerning the inflexibility issue. One contention is that the Delaney Clause is too restrictive, allowing FDA no discretion in situations where a substance is

determined to be a carcinogen. The counterargument is that the Clause allows the FDA Commissioner discretion regarding the appropriateness of testing procedures and data interpretation in the determination of carcinogenicity of a food substance. Food safety experts we interviewed disagreed as to whether the Delaney Clause presented FDA with a major regulatory dilemma.

A second issue is whether the Delaney Clause has affected other Federal agencies' regulatory policies. Although no other agency has similar legislation, industry representatives, in articles and speeches, have contended that the Clause's "no-risk" philosophy influences the regulatory actions of the other agencies. One industry representative described the Delaney philosophy as requiring that the exposure to any level of a carcinogen, regardless of dose, shall be reduced to the lowest technically feasible level and to zero if a suitable alternative exists. More than half of the experts said that the Clause has had an impact on regulatory action taken in other Federal agencies. They stated that EPA, OSHA, and CPSC have been influenced by the no-risk philosophy. They noted that the Clause was the forerunner of these other agencies' legislation and that their actions reflect an attempt to establish zero exposure goals. Again, opinion on this issue was split. The table below summarizes the responses on these two questions:

Impact on Federal Agencies (note a)

	The Delaney Clause presents a regulatory dilemma to FDA			The Delaney Clause affects other Federal agencies		
	Yes	No	No response (note b)	Yes	No	No response (note b)
Former FDA Commissioners and General Counsels	5	3	1	7	-	2
Biomedical researchers	8	7	-	6	4	5
Consumer group representatives	1	5	-	2	2	2
Food and chemical companies and trade associations	17	3	1	18	-	3
	31	18	2	33	6	12

a/See note a, p. 22.

b/This column includes food safety experts who did not respond to or had no basis to make a judgment on the issue.

Views on FDA's regulatory dilemma

Former FDA regulators commented that:

--Increasing use of indirect additives will be a future source of problems because these additives, which are used in packaging, adhesives, and equipment used to process and store food, become components of food by migrating or leaching into food. These substances could never be considered for use as direct additives because experimental evidence would suggest they are probably toxic. Many may be carcinogenic.

--Advances in analytical chemistry have enabled scientists to detect in food traces of packaging materials that were once thought incapable of migrating. Thus, the number of potential indirect food additives has enlarged.

--Another saccharin-like situation will occur.

The biomedical researchers observed that:

--The Delaney Clause is too inflexible, especially in its failure to consider benefits, its lack of opportunity to rebut evidence of carcinogenicity (see p. 42), and its effect on indirect additives which may not pose a human health hazard.

The consumer group representatives argued that:

--FDA has sufficient scientific discretion.

--Substitutes are available for the great majority of food additives.

--The Delaney Clause is not a problem because it is not used.

However, the food and chemical companies and trade associations analyzed the situation differently. Their comments centered on one issue:

--The Delaney Clause is too inflexible.

Views on effects on other agencies

The former FDA regulators commented that:

--The Delaney Clause concept has been emulated by other Federal agencies.

--The Clause is an exceedingly important symbol. It has had a psychological effect beyond FDA to EPA, OSHA, etc.

Biomedical researchers observed that:

--The Delaney Clause has influenced other Federal agencies to adopt more stringent regulatory standards.

--Other Federal agencies are trying to reduce exposure to carcinogens to zero.

--The Clause is a symbol of the Government's position. If it were removed, other agencies might relax their standards.

Consumer group representatives noted that:

--The Delaney Clause may serve as a standard for other agencies but it has had no significant impact.

Industry representatives said that:

--The Delaney Clause has affected other Federal agencies when they set up environmental or workplace controls.

--The Clause has waved a "red flag" at carcinogens, and other agencies have followed FDA's lead.

PUBLIC OPINION REGARDING THE USE OF CARCINOGENIC FOOD ADDITIVES

We identified 12 public opinion polls conducted over the past 10 years which addressed the question of food safety. While none of the polls specifically dealt with the Delaney Clause, a number of them showed that the public is concerned about cancer-causing food and color additives.

The level of concern exhibited by those polled changed as some substances became controversial. For example, the 1977 saccharin controversy raised both the public's level of worry about food additives and their dissatisfaction with Federal regulatory policy. About 50 percent of those polled have consistently expressed concern about the safety of food and color additives in general. When questioned about specific substances, however, people wanted individual freedom of choice--a contradiction to their response when the question is phrased without reference to a particular food additive.

Recent polls show contradictory attitudes

Four recent polls have focused on the problems of regulatory choices for cancer-causing food and color additives.

A 1980 federally funded national opinion survey found that public views on Government regulation regarding chemicals showed

80 to 90 percent of the respondents favoring some Government control, with the percentages favoring warning labels on packages and outright bans varying by chemical.

Forty-seven percent wanted to ban a carcinogenic color additive, 33 percent wanted to ban a carcinogenic food additive, and only 16 percent wanted to ban saccharin. Warning labels for color additives, food additives, and saccharin were favored by 44, 57, and 66 percent, respectively.

A 1980 U.S. Department of Agriculture poll queried the public concerning its views on safety of food additives and the Government's policy. When asked what the Government should do if scientific tests found that an essential ingredient which was ingested regularly produced cancer in laboratory animals, 36 percent 1/ wanted to ban the ingredient. Other suggestions showed that 57 percent wanted to continue testing, 55 percent wanted a package warning label, 47 percent wanted to publish more information, and 24 percent wanted to limit the ingredient's use.

"Risk in a Complex Society," a Louis Harris and Associates public opinion survey, involved interviews with five sample groups. 2/ These groups were asked about their preferred course of action when potentially carcinogenic food additives were discovered in food. Business, financial, and Government leaders agreed that society should decide each case separately, banning in some situations and letting people decide for themselves in others. The public was opposed to product bans and supported freedom of choice. Only 1 and 2 percent of top business executives and bankers, respectively, wanted to ban carcinogenic food additives on principle. All the groups surveyed supported the concept of making decisions on a case-by-case basis.

An overwhelming majority (from 77 to 86 percent) of the four leadership groups envisioned cost-benefit analysis as a tool to determine the benefits and costs of regulatory efforts to control risks.

The poll showed that the public is confident that the medical/scientific community is doing the best job of making society "acceptably safe." Similarly, 60 percent of the four leadership groups gave a high rating to FDA for its performance

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1/Many respondents gave multiple answers.

2/Corporate officers, institutional investors and corporate bankers, Members of Congress or their aides, members of Federal regulatory agencies, and adult members of the public.

in protecting the public. FDA was rated first among the Federal regulatory agencies.

The public's attitudes toward cancer were perhaps most exhaustively researched in a survey by Cambridge Reports, Inc. This study showed that the public has conflicting attitudes toward the use of cancer-causing substances in food. The public endorsed the idea that a cancer-causing substance should be permitted if it has "real" benefits, but they also endorsed a version of the Delaney Clause that sets a strict ban on all cancer-causing substances.

For example, 49 percent of those polled believe that no substance or chemical should be permitted to be sold for use in food if it is found to cause cancer when consumed in any dosage by humans or animals. However, 59 percent thought that possible cancer-causing food additives should be permitted if they have real social benefits. Two-thirds of the respondents wanted the right to make individual risk-benefit decisions on whether to use a cancer-causing chemical; 22 percent wanted to ban.

Respondents defined "risks" and "benefits" differently. A plurality defined "risk" as taking a chance, particularly a chance with your health in the case of a carcinogen. "Benefit" implied coming out ahead, making a net gain, particularly in terms of improved health or a longer life. Fifty percent of the participants agreed that some risk must always be incurred if any significant benefits are sought, and 31 percent believed that no benefit can outweigh the risk involved when cancer is concerned. To make an intelligent decision, one must be able to evaluate the risks with which one deals. Two-thirds of those polled stated that they personally do not know enough to evaluate the possible cancer risks of chemical substances.

In an attempt to sort out the contradictory positions taken by the public, the polling organization asked respondents to react to two specific cases--the bans on saccharin and food dyes. Both substances are seen as carcinogenic. One quarter of the public is willing to ban both, one quarter wants no ban at all, and about half is in the middle. According to the pollster, this middle group is inclined to make individual risk-benefit decisions regarding carcinogens. Eighty-two percent supported truth in labeling 1/ as an alternative to banning.

1/The description of truth in labeling was: Companies should state in plain English what the possible dangers are in a product, as they do in a cigarette package, and then leave it to the individual consumer to decide whether or not to use that product.

In summary, consumers approve of a ban in the abstract but are opposed to banning substances like saccharin, which have been in use for years.

CONCLUSIONS

The Delaney Clause has been and continues to be a source of controversy and a target for change. Although banning cancer-causing substances to the food supply is theoretically desirable, it may not be practical. Scientific advances since 1958 have resulted in many food safety experts questioning the Delaney Clause "zero-risk" philosophy. Suggestions for legislative change have not produced an alternative regulatory framework on which food safety experts agree. Models for analyzing data on risks and benefits and weighing them against each other must be refined and improved. Such issues as what is an acceptable level of risk and what benefits, if any, should be considered in any decisionmaking framework must be dealt with and will continue to provide a challenge for policymakers concerning the regulation of food additives.

CHAPTER 4

FEDERAL LAWS SET DIFFERENT REGULATORY POLICIES FOR DIFFERENT USES OF CANCER-CAUSING SUBSTANCES

Cancer-causing substances are regulated differently within FDA, as well as among FDA and other Federal agencies, based upon different social, economic, and health considerations. (See app. IV.) Under the FD&C Act, not all substances added to food are regulated as food additives. The Delaney Clause prohibition against the use of carcinogens does not apply to food substances that are prior sanctioned, natural constituents, or food contaminants. Similarly, Federal laws that regulate pesticides, environmental contaminants, consumer products, and hazardous substances in the workplace do not require that carcinogens be banned. Instead, these Federal laws--administered by EPA, OSHA, and CPSC--require the risk from exposure to carcinogens to be balanced against one or more of the following factors: health, social, economic, and environmental benefits; costs to the consumer and industry; and technological feasibility.

Under these laws, cancer-causing substances are regulated no differently than other toxic chemicals. Federal agencies may use one of several options in regulating the use of cancer-causing substances, including allowing unrestricted use, banning, setting tolerance levels, or requiring the use of protective clothing or labeling.

DIFFERENT RISK-BASED CRITERIA USED IN REGULATING FOOD SUBSTANCES

FDA applies different safety standards in regulating cancer-causing substances intended for human food use, including food additives, color additives, animal drugs, natural constituents, food contaminants, and substances that are GRAS or prior sanctioned. The Delaney Clause is the ultimate example of regulation based on health risk. It prohibits the approval of any food additive found to induce cancer in animals or humans. While health risk is the primary consideration in regulating all food substances, the FD&C Act allows FDA to consider the availability of food in regulating some food substances that are not food additives.

Regulation of food additives

FDA establishes regulations for substances used in food and defined as food additives. The general safety clause of the act prohibits FDA from approving a food additive if scientific and

other data fail to establish that the proposed use of the additive will be safe--i.e., there is reasonable certainty that no harm will result from the proposed use of the additive. The Delaney Clause provides an extra safeguard against the approval of food additives that cause cancer. Once a food additive is found to be a carcinogen, it must be banned. A finding that there is a reasonable certainty that no harm will result from its proposed use is impossible. Indirect food additives, which are substances that get into food indirectly through production methods, manufacturing processes, or packaging, are regulated the same as direct food additives.

In considering a proposed food additive, FDA may prohibit its use, allow its unrestricted use, or require a tolerance level, which is the maximum amount of a substance which can be safely used and still accomplish its intended purpose.

Regulation of color additives

The 1960 Color Additive Amendments to the FD&C Act (Public Law 86-618) establish a system of premarket clearance for color additives intended for use in foods, drugs, or cosmetics. Under this system, FDA establishes by regulation the conditions under which color additives may be safely used. Like the Food Additives Amendment of 1958, the Color Additive Amendments state that a color additive is deemed unsafe if it induces cancer in humans or animals.

In determining a color additive's safety, FDA considers the same factors it uses for food additives (see p. 4). In addition, FDA considers the availability of practicable methods of analysis for determining the identity and quality of (1) the pure dye and all intermediates and other impurities contained in the color additive, (2) the additive in food, drugs, or cosmetics, and (3) any substance formed in such products because of the use of the additive.

The Color Additive Amendments permitted FDA to list provisionally color additives in use at the time the amendments were passed to allow completion of scientific studies to determine their safety. A substance's provisional listing is terminated when FDA determines that public health is endangered or when it permanently lists the substance.

Regulation of substances given to food producing animals and pesticide residues

FDA also regulates substances given to animals intended for human food use. These substances include (1) ingredients in animal feed, (2) animal drugs, and (3) color additives. The FD&C

Act provides that cancer-causing substances may be used if the substances will not adversely affect the animals and no residue will be found in any food yielded by or derived from the animals.

The FD&C Act also provides that, in the case of addition of a pesticide which may be poisonous or deleterious, regulations should be promulgated to limit the quantity of such substances on raw agricultural commodities.

Regulation of substances that are prior sanctioned or GRAS

Substances classified as prior sanctioned or GRAS are specifically exempted from the act's food additive provisions.

--Prior sanction substances are those substances used in food in accordance with sanctions or approvals granted by FDA or the Department of Agriculture before enactment of the 1958 Food Additives Amendment.

--Substances classified as GRAS are substances that experts have found through scientific evidence or experience based on common use in food to be safe when used as intended.

Prior sanction substances found to cause cancer are subject to the adulteration provisions of section 402 of the FD&C Act--food is adulterated if it contains any poisonous or deleterious substance that may render it injurious to health. To take action against a substance that is prior sanctioned, FDA has the burden of proving that the substance may be potentially harmful.

A GRAS substance found to cause cancer would no longer be recognized as safe and therefore would no longer be exempt from the act's food additive provisions. As a food additive, such a substance would be subject to the Delaney Clause. FDA used this approach in its regulation of saccharin. As a result of questions raised about saccharin's potential to cause cancer, FDA in 1972 removed saccharin from the GRAS list and issued an interim food additive regulation permitting limited use of the substance. Interim food additive regulations are issued when new information raises questions of safety and remain in effect until the questions raised are resolved by further study.

After test results confirmed that saccharin caused bladder cancer in animals, FDA in April 1977 proposed to repeal the interim regulations and prohibit the use of saccharin as a food additive, relying on both the general safety clause and the Delaney Clause. The Congress, in November 1977, placed a moratorium on the proposed ban, pending completion of further studies. The Congress extended the moratorium in June 1980. In August 1981 it was again extended, this time for 2 years.

Regulation of natural constituents of food

Natural food constituents are subject to different safety standards than food additives. Under the FD&C Act's adulteration provisions, FDA determines if a naturally occurring poisonous or deleterious substance is present in food in an amount that may ordinarily present a serious health risk. If so, FDA may require the removal of the adulterated substance from the food supply.

FDA officials told us that, in regulating natural constituents, FDA also considers the benefit of the substance and the impact a prohibition would have on the available food supply. For instance, they said that FDA would probably not remove from the food supply a deleterious substance that is a nutrient, widely used, and entrenched in the food system, unless it posed a significant health risk.

Regulation of food contaminants

FDA may establish tolerances for added poisonous or deleterious substances (food contaminants) that are required in the production of food or that cannot be avoided by good manufacturing practices. At levels below the established tolerance, the food will not be considered adulterated. In establishing tolerances, the act requires FDA to consider other ways that consumers may be affected by the same or other poisonous or deleterious substances.

FDA may also establish action levels for food contaminants. Unlike tolerance levels, action levels are not set through formal rulemaking procedures and serve only as guidelines to manufacturers. They are used as alternatives to tolerance levels when

--information about risks is tentative,

--quick regulatory action appears necessary,

--technological or industrial changes are expected to reduce contamination in the near future, or

--a long-term regulatory approach has not yet been decided.

In 1965 FDA set an action level of 30 parts per billion (ppb) for aflatoxin, a potent carcinogen produced by a fungus found primarily on corn and peanuts. In 1969 the action level was reduced to 20 ppb, and in 1974 FDA proposed a tolerance level of 15 ppb, which is still pending. In determining these levels, FDA considered the economic and technological feasibility of reducing the contamination. According to FDA, aflatoxin was not banned because a substantial portion of the world's food supply would have been destroyed.

FDA regulatory action against carcinogens or suspected carcinogens

Before enactment of the 1958 Food Additives Amendment, FDA banned three substances added to foods because of actual or suspected carcinogenicity--thiourea (used to prevent the browning of fruits) in 1948, and dulcin and P-4000 (artificial sweeteners) in 1950. In all three cases, FDA took action under the adulteration provisions of the FD&C Act. Since 1958, FDA has banned nine food substances on findings or suspicion of carcinogenicity. In two cases, FDA invoked the Delaney Clause--in 1967 to ban Flectol H, and in 1969 to ban chloranaline. Both substances were indirect additives used in food packaging adhesives. FDA used the general safety clause and the adulteration provisions to ban safrole, a flavoring compound, in 1960; oil of calamus, a flavoring compound, in 1968; and cyclamate, an artificial sweetener, in 1969.

FDA acted under the general safety clause to ban two suspected cancer-causing food additives--diethylpyrocarbonate (a ferment inhibitor in beverages) in 1972 and mercaptoimidazoline (used in rubber products that may come into contact with food) in 1973. FDA also banned two color additives for use in food on the basis of suspected carcinogenicity--Violet No. 1 in 1973 and Red No. 2 in 1976. Because both additives had been provisionally rather than permanently listed under the 1960 Color Additive Amendments, the Delaney Clause did not apply. Instead, FDA terminated the provisional listings on the basis that these actions were necessary to protect the public health.

Since 1958 FDA has also proposed to remove from use in food the following carcinogens or suspected carcinogens:

--Saccharin, in April 1977, based on the general safety and the Delaney Clause.

--Chloroform, a solvent used in manufacturing food packaging materials, in April 1976, based on the Delaney Clause.

--Trichloroethylene, a solvent used in the manufacture of decaffeinated coffee, in September 1977, based on the Delaney Clause.

--Morpholine, a substance added to boiler water in the preparation of steam that will contact food, in November 1972, based on the adulteration provisions of the FD&C Act.

--Vinyl chloride monomer, a substance used to produce food packaging material and a suspected carcinogen, in September 1975, based on the adulteration provisions of the FD&C Act.

These proposed bans are still pending.

RISK-BENEFIT COMPARISONS REQUIRED FOR PESTICIDES, TOXIC SUBSTANCES, AND CONSUMER PRODUCTS

The Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136 et seq.) and the Toxic Substances Control Act (15 U.S.C. 2601 note) (TSCA), administered by EPA, and the Consumer Product Safety Act (15 U.S.C. 2051 note), administered by CPSC, require risk-benefit evaluations for regulating cancer-causing pesticides, toxic substances, and consumer products. Under these laws, carcinogens are regulated no differently than other hazardous substances. Agencies may (1) allow unrestricted use of the substance, (2) set standards to limit the use of the substance, or (3) ban the use of the substance.

These laws require the agencies to determine what the potential risk will be from the use of the regulated substance. Other factors which are considered, and which differ for each law, include: (1) economic, social, and environmental costs and benefits, (2) effects on the national economy and small businesses, technological innovation, and public health, (3) utility, (4) the availability of substitute products, and (5) changes in aesthetics.

EPA considers economic, social, and environmental costs and benefits in regulating pesticides

The Federal Insecticide, Fungicide, and Rodenticide Act requires EPA to register pesticides which pose no "unreasonable adverse effects" to the environment, taking into account the economic, social, and environmental costs and benefits of the pesticide's use. EPA may approve, ban, or limit use of pesticides.

While EPA recognizes that there is no threshold for carcinogens, it also believes that eliminating all risk from chemical carcinogens is not possible without unacceptable social and economic consequences. In a May 25, 1976, Federal Register Notice of EPA's procedures and guidelines for regulating suspected carcinogens, the EPA Administrator stated that the concept behind the act was to "eliminate or reduce exposure to the greatest extent possible consistent with the acceptability of the cost involved." Presently, EPA is reviewing its cancer policy to determine if new scientific findings may support policy modifications for specific agents.

EPA instituted the rebuttable presumption against registration program, which weighs risks and benefits of potentially hazardous pesticides to determine human health risks and the

regulatory action necessary to protect the public and the environment. Under this program, EPA publishes in the Federal Register its preliminary position on the potential risk of a pesticide. Manufacturers producing or proposing to produce the pesticide may submit proof that exposure to the pesticide does not cause the effects described or that the study or studies supporting the presumption are not scientifically valid.

If no rebuttal information is submitted or if the submitted information fails to rebut the presumption, EPA weighs the risks and benefits associated with use of the pesticide, including an evaluation of available alternatives. In doing so, EPA considers:

--Health risks, which are measured by the increased number of individuals expected to suffer an adverse effect through a lifetime of exposure to the pesticide.

--Environmental risks, which are the pesticide's effects on nontarget plants and insects, on microorganisms, and on aquatic, terrestrial, and avian organisms.

--Economic impact on users, consumers, and production and prices of commodities or services.

EPA officials told us that decisions on whether risks outweigh benefits--and thus when a pesticide should be banned--are based on their best judgment and experience. These officials added that EPA uses caution in banning a pesticide because the use of an alternative pesticide could ultimately be even more hazardous.

EPA attempts to reduce exposure to the extent that risks outweigh benefits. For example, as a result of EPA's first full-scale risk-benefit review under the rebuttable presumption against registration program, in February 1979 EPA banned chlorobenzilate, a carcinogen, for all uses except citrus fruit uses in Florida, Texas, California, and Arizona and restricted its use to persons who are certified applicators or under the supervision of certified applicators. EPA noted that the loss of chlorobenzilate would result in increased use of other pesticides--some more hazardous than chlorobenzilate--and that, without the product, the four States would have to spend an additional $28 million to $57 million a year for other pesticides. EPA also required that precautions concerning chlorobenzilate's use be specified on the product label and that protective clothing, gloves, and a respirator be worn.

As a result of another risk-benefit analysis, in October 1979 EPA decided to allow the continued use of pronamide, a cancer-causing pesticide applied to such crops as lettuce, alfalfa, and berries, but attempted to reduce exposure by

--classifying the product as a restricted pesticide that can be purchased and used only by certified applicators;

--requiring precautions concerning pronamide's use to be stated on the product's label and protective clothing, gloves, and boots to be worn while using the product; and

--requiring the manufacturer to package the wettable powder in water-soluble bags and to protect mixers who oper. the packages from unnecessary exposure to risks of breathing pronamide dust.

EPA considers economic, technological, health, and environmental factors in regulating toxic substances

TSCA, enacted in 1976 to protect the public health and the environment from unreasonable chemical risks, requires EPA to weigh benefits and risks in regulating hazardous chemical substances and mixtures and to consider the "effect on the national economy, small businesses, technological innovation, the environment, and public health." Under TSCA, EPA may regulate the manufacture, processing, distribution in commerce, use, or disposal of a toxic chemical.

Under TSCA, EPA can require manufacturers who wish to continue marketing existing chemicals or new uses of existing chemicals to test for adverse health and environmental effects. Manufacturers wanting to introduce new chemicals may also be required to perform tests. A committee composed of persons appointed by certain Federal agencies can also recommend to EPA chemicals for testing, giving priority to carcinogens and other toxic chemicals. About 55,000 chemicals which are manufactured or imported for commercial purposes in the United States are potentially subject to TSCA. However, the act requires, in most cases, that other Federal laws controlling toxic chemicals take precedence over TSCA.

CPSC considers product utility, availability of substitute products, and cost in regulating consumer products

The Consumer Product Safety Act requires CPSC to balance risks and benefits in setting standards for preventing or reducing an unreasonable risk of injury from use of a consumer product. Unreasonable risk of injury is determined by balancing the benefits of a reduction in health risk against the impact of regulation on the product's utility, the availability of substitute products, and the cost of regulation. Cost factors include economic costs to the consumer and industry, environmental impacts, and changes in aesthetics. The act requires CPSC to ban the use of a hazardous

product only when such product presents an unreasonable risk of injury and a consumer product safety standard is not feasible.

CPSC does not rely solely on quantified cost-benefit analyses in regulatory decisionmaking. A December 30, 1980, notice of proposed rulemaking in the Federal Register stated that the Commission believes that the ultimate issues involved in issuing health and safety regulations are likely to require value judgments as much as numerical judgments. As of February 1981, CPSC had not set any standards for the allowed use of carcinogens. Under the Consumer Product Safety Act, CPSC has banned vinyl chloride monomers and asbestos when found in certain consumer products. In addition, CPSC proposed to ban benzene in certain products but withdrew the proposal because of its declining use.

CPSC also administers the Federal Hazardous Substances Act, which it has interpreted as allowing risk-benefit analyses. CPSC can ban or require manufacturers to label hazardous substances that may cause substantial illness from use and must ban toys or articles considered dangerous for use by children. Under the act, tris, an animal carcinogen, was banned from children's sleepwear because it was determined to be a hazardous substance.

TECHNOLOGICAL FEASIBILITY EVALUATIONS REQUIRED FOR AIR AND WATER POLLUTANTS AND OCCUPATIONAL HAZARDS

Federal laws require technological feasibility to be considered in reducing exposure from carcinogens in the air, water, and workplace. The Clean Air Act (42 U.S.C. 7401 et seq.), the Federal Water Pollution Control Act (33 U.S.C. 1251 et seq.), and the Safe Drinking Water Act (42 U.S.C. 300f et seq.), administered by EPA and the Occupational Safety and Health Act (29 U.S.C. 651 et seq.), administered by OSHA, do not require carcinogens to be regulated more stringently than other environmental and occupational contaminants.

EPA considers best available control technology in regulating air and water pollutants

EPA establishes nationwide emission standards for all hazardous air pollutants based upon the best available control technology. Standards must provide an ample safety margin to protect the public health. While EPA's goal is to reduce exposures to cancer-causing substances to the maximum extent, EPA has stated that zero-emission requirements would lead to the closing of many facilities which emit cancer-causing air pollutants. EPA also identifies toxic water pollutants and develops nationwide effluent limitations for each, based on the best available technology economically achievable.

In addition, EPA sets maximum contaminant levels for substances in drinking water which may adversely affect people's health. EPA sets levels based on health risks and the technological and economic feasibility of removing contaminants from the public water supply.

OSHA considers best available or projected control technology in regulating workplace hazards

OSHA sets health and safety standards for the workplace that are expected to provide the highest feasible degree of protection for the employee. The Occupational Safety and Health Act does not explicitly authorize OSHA to ban workplace carcinogens. OSHA considers the feasibility of the standards, in addition to the attainment of the highest degree of health and safety protection for the employee, and determines the lowest feasible exposure level based upon the best available or projected technology and its cost.

Standards set levels of exposure and may require medical monitoring, changes in work practices, engineering controls, or protective clothing. On January 22, 1980, OSHA issued a rule for identifying, classifying, and regulating carcinogens which (1) sets forth criteria for the types of scientific tests needed to assess carcinogenicity, (2) sets up a classification scheme for carcinogens, based on available data and exposure in the workplace, and (3) establishes a system for prioritizing carcinogens so that the 10 "worst" will be considered for regulation. Some of the factors that OSHA considers in priority-setting are

--the estimated number of exposed workers,

--the estimated levels of their exposure,

--the molecular similarity of the substance to a known carcinogen, and

--the availability of safe substitute substances.

The Supreme Court, in its July 1980 benzene decision, 1/ upheld a lower court ruling that OSHA does not have the discretion to adopt standards designed to create absolutely risk-free workplaces. OSHA had stated that benzene caused leukemia (a cancer of the white blood cells). In this case OSHA tried to lower the

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1/Industrial Union Department, AFL-CIO v. American Petroleum Institute, et al. 100 S. CT. 2844 (1980).

permissible level of benezene in the workplace from 10 parts to 1 part per million. The Court ruled that OSHA must show that a toxic substance poses a significant health risk in the workplace and that a new lower standard is reasonably necessary or appropriate to provide safe or healthful employment or places of employment.

CONCLUSIONS

Various Federal laws establish different criteria for regulating cancer-causing substances. Unlike the "zero-risk" philosophy of the Delaney Clause, these laws give agencies a flexible regulatory approach tailored to the risks and uses associated with a particular substance. Agency decisions on the use of cancer-causing substances are not directed at achieving absolute safety or eliminating all health risk. Rather, agency regulators consider the utility and availability of a particular substance and balance identified risks against certain social, health, and economic factors. Agencies recognize that certain cancer-causing substances cannot be banned from the workplace, the environment, and consumer products without some adverse consequences. These regulatory approaches can serve as a useful starting point for discussion of alternatives to the Delaney Clause.

CHAPTER 5

ALTERNATIVES TO THE DELANEY CLAUSE

Most of the food safety experts and regulatory agency officials we spoke with believe that the Delaney Clause should be changed. Also, three organizations presented alternative approaches to the Clause. However, there is no unanimity about how it should be changed. In establishing policy for the regulation of food additives, three obvious alternatives are possible: (1) leave the Delaney Clause unchanged, (2) delete it from the FD&C Act, or (3) amend it. If the Clause were to be amended, the three options that seemed to have the most support from food safety experts and regulatory agency officials were: (1) set an acceptable level of risk, (2) compare risks and benefits, and (3) compare the health risk of using a carcinogen with the health risk of not using it. Various alternatives are discussed below.

LEAVE THE DELANEY CLAUSE UNCHANGED

The alternative of leaving the Delaney Clause unchanged would require no action by either the Congress or FDA. A substance found to be a carcinogen would be banned. This alternative provides the maximum protection to food consumers. FDA would require no additional resources beyond what would otherwise be needed. Controversy over the adequacy of testing methods would continue. However, FDA would not be required, as part of its regulatory responsibility, to estimate the risk to humans from a carcinogenic food additive. The Congress would, of course, still have the option to enact legislation overruling any regulatory action by FDA to ban carcinogens.

DELETE THE DELANEY CLAUSE FROM THE LAW AND REGULATE CARCINOGENS UNDER THE GENERAL SAFETY CLAUSE

A second alternative would be to delete the Delaney Clause from the law and regulate carcinogens under the general safety clause. Under this alternative, food additives found to be carcinogenic would not automatically have to be banned. FDA would apply the same standards of safety as it does for noncarcinogenic food additives. Food additive sponsors would need to show that there was a reasonable certainty that no harm would come from the proposed use of the substance. Controversy would still exist under this alternative since the accuracy of long-term animal tests and methods of extrapolation from animals to humans would continue to be questioned. A further problem to be dealt with is the Delaney Clause philosophy that there is no threshold for carcinogens; that is, there is no level below which a carcinogen will not cause cancer.

At the time of passage of the Food Additives Amendment, the Department of Health, Education, and Welfare and FDA took the position that the Delaney Clause did not increase the amount of consumer protection provided by the general safety clause of the amendment. The Department expressed the view that the general safety provisions of the amendment would preclude the approval of a carcinogenic food additive.

Since passage of the Food Additives Amendment, FDA has invoked the Delaney Clause only twice, but has banned a number of food and color additives that were suspected carcinogens. In these cases, FDA relied on the general safety clause of the Food and Color Additive Amendments or on other provisions in the Color Additive Amendments (see p. 41). In two well-known cases, cyclamates and Red No. 2, FDA banned the subtances because they were suspect (but not proven) carcinogens.

AMEND THE DELANEY CLAUSE

The third alternative for the regulation of carcinogenic food additives would be to amend the FD&C Act. Three options appear to have the most support: risk-based (set an acceptable level of risk), risk-benefit (compare the risks from using a carcinogen with the benefits derived from its use), and risk-risk (compare the health risk from using a carcinogen with the health risk from not using it). Each of these options is discussed below.

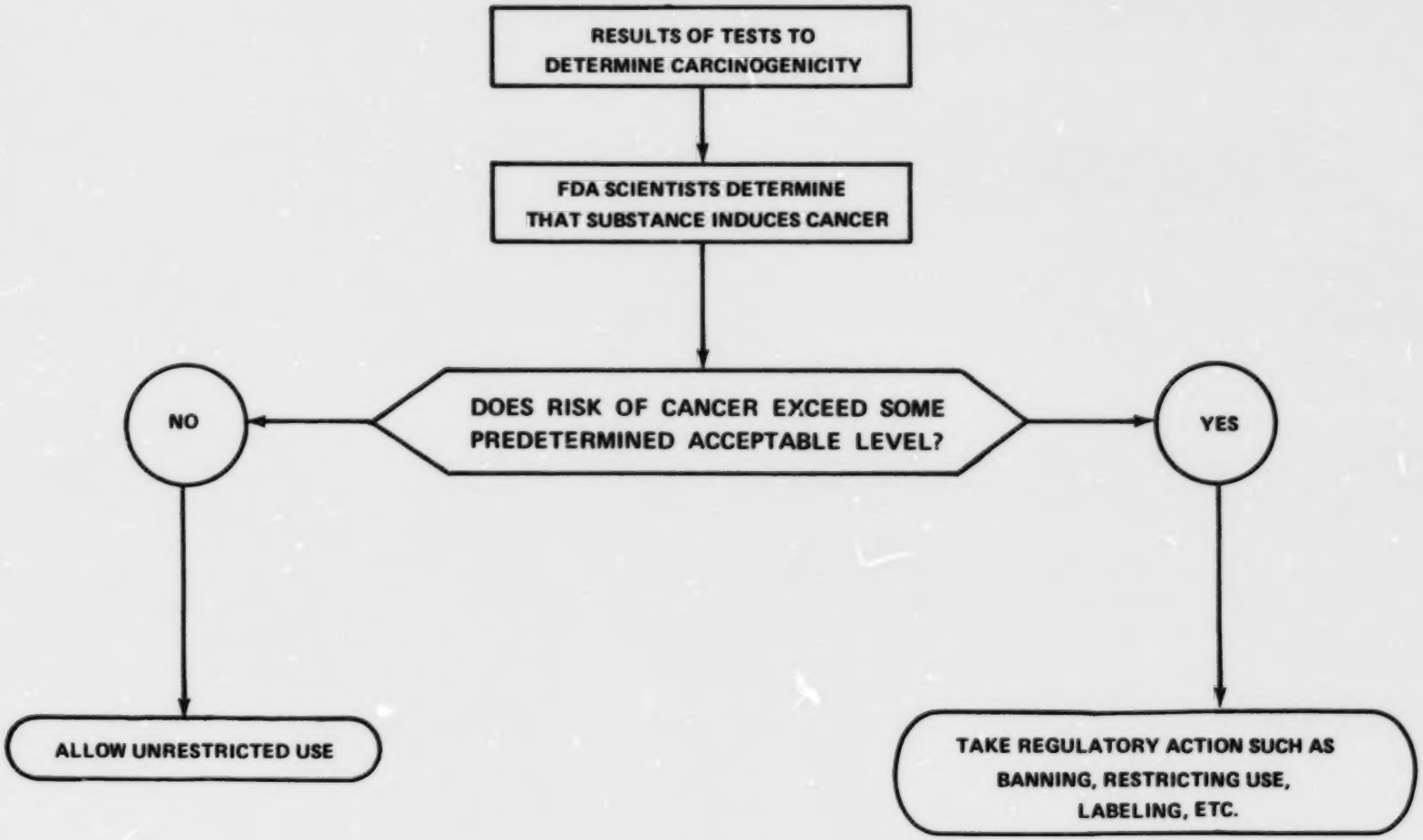
Risk-only option

Under this option, the Congress could enact legislation requiring FDA to ban a carcinogenic food additive only when FDA determines that the risk imposed is greater than some predetermined level. In considering this option the Congress needs to be aware that different mathematical models for estimating human risk can produce widely varying results which may differ by many orders of magnitude. (See p. 17.) The model on page 50 outlines this decisionmaking process.

This option would allow FDA to reach a determination that the estimated health risk from the use of a substance would not be significant or that it would be acceptable. Most of FDA's Bureau of Foods officials we spoke with favored this approach. They believed that the increased flexibility provided in this option would allow them to use their training and experience to evaluate the potential risk of carcinogenicity from a food additive. These officials believed that they could review the toxicological data developed in animal bioassays and determine whether the risk of cancer would be significant.

BEST DOCUMENT AVAILABLE

EVALUATION OF RISK


RESULTS OF TESTS TO DETERMINE CARCINOGENICITY
FDA SCIENTISTS DETERMINE THAT SUBSTANCE INDUCES CANCER
DOES RISK OF CANCER EXCEED SOME PREDETERMINED ACCEPTABLE LEVEL?
NO
YES
ALLOW UNRESTRICTED USE
TAKE REGULATORY ACTION SUCH AS BANNING, RESTRICTING USE, LABELING, ETC.

The negative aspects of this approach include:

--Consumers might be exposed to some carcinogenic food additives.

--Additional resources may be needed by FDA's Bureau of Foods. The associate director for toxicological sciences, Bureau of Foods, estimated that about 15 to 20 personnel would be needed to make the type of analysis necessary to assess risks.

--Questions concerning the adequacy of animal tests and the accuracy of risk assessment would continue to exist and be a source of controversy. (See ch. 2.)

--FDA decisions concerning carcinogenic food additives would be controversial and likely the subject of civil suits by whatever parties disagreed with FDA.

Risk-benefit option

Under this option FDA would, in addition to assessing risk, also be required to measure the benefits that accrue from the use of carcinogenic food additives. The risks would then be balanced against the benefits and a determination made as to whether the substance should be allowed in foods. The model on page 52 outlines this decisionmaking process.

A wide range of benefits could be considered, including:

--Economic - Does the use of the substance allow food to be produced and distributed at lower cost?

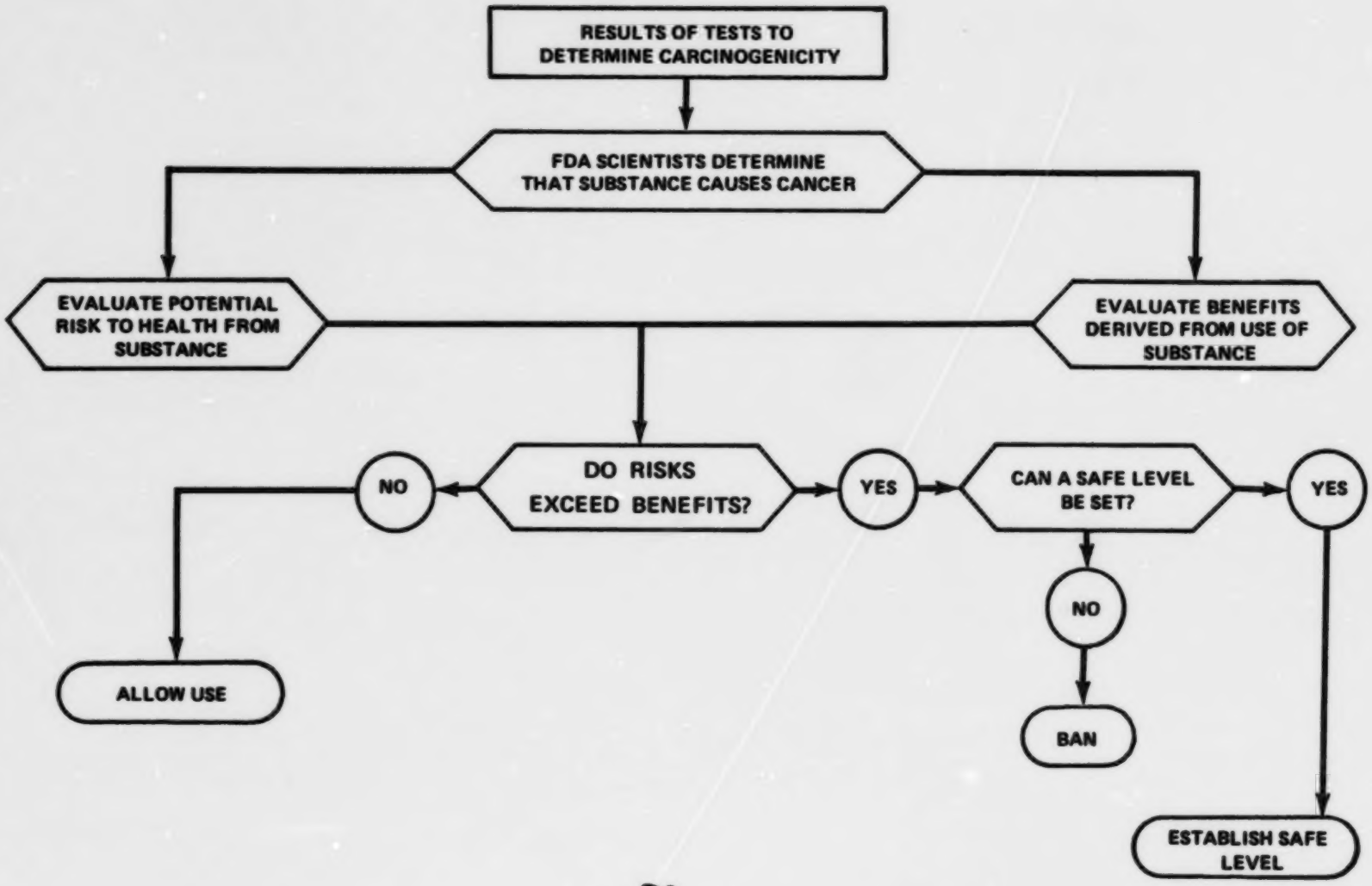
--Health - Does the use of the substance provide some essential nutrient?

--Other - Does the use of the substance provide other benefits, such as enhancing flavor or appearance, increasing the supply of food, or making food preparation, storage, or distribution safe or more convenient?

The results of FDA's regulatory decisionmaking would probably remain controversial, particularly since there would be a need to not only assess risks and benefits individually but also compare the risks and benefits. FDA, based on this comparison, would then have to decide the proper regulatory action.

All of the advantages of the risk-only option plus the added flexibility and limitations inherent in the risk-benefit assessment would exist. FDA, which does not currently consider the

EVALUATION OF RISK-BENEFIT



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benefits of food additives, would probably need additional personnel to make these analyses.

Risk-risk option

FDA, under this option, would determine the risks inherent in the proposed use of a carcinogenic food additive. It would also determine whether there were any risks associated with a prohibition on the use of the additive. The model on page 54 outlines this decisionmaking process.

An example of a food additive for which benefits are asserted is nitrite, which is used in meat as a preservative and flavor additive. Nitrite also retards the growth of bacteria, which under certain conditions can produce the deadly toxin responsible for food poisoning known as botulism. In 1978 a study conducted at the Massachusetts Institute of Technology raised questions about the possible carcinogenicity of nitrites. Later reviews raised concerns about the validity of this study, and FDA was not required to ban nitrites. The case of nitrites, however, points up an example of a possible regulatory dilemma that could confront FDA.

Under a risk-risk option, FDA would be required to balance these risks and determine the best regulatory option available. That is, would a ban or other restriction of a carcinogenic food additive result in more risks to health than would allowing its use? This option would generally have the same advantages and disadvantages as would a risk-only option. The need for reliance on animal tests and extrapolation methods for determining the risk to humans would exist, along with a need to balance these risks against the risk associated with banning or otherwise regulating the substance.

ALTERNATIVES SUGGESTED BY THE COUNCIL FOR AGRICULTURAL SCIENCE AND TECHNOLOGY

The Council for Agricultural Science and Technology (CAST) 1/ prepared and issued a report 2/ which discusses (1) the adequacy

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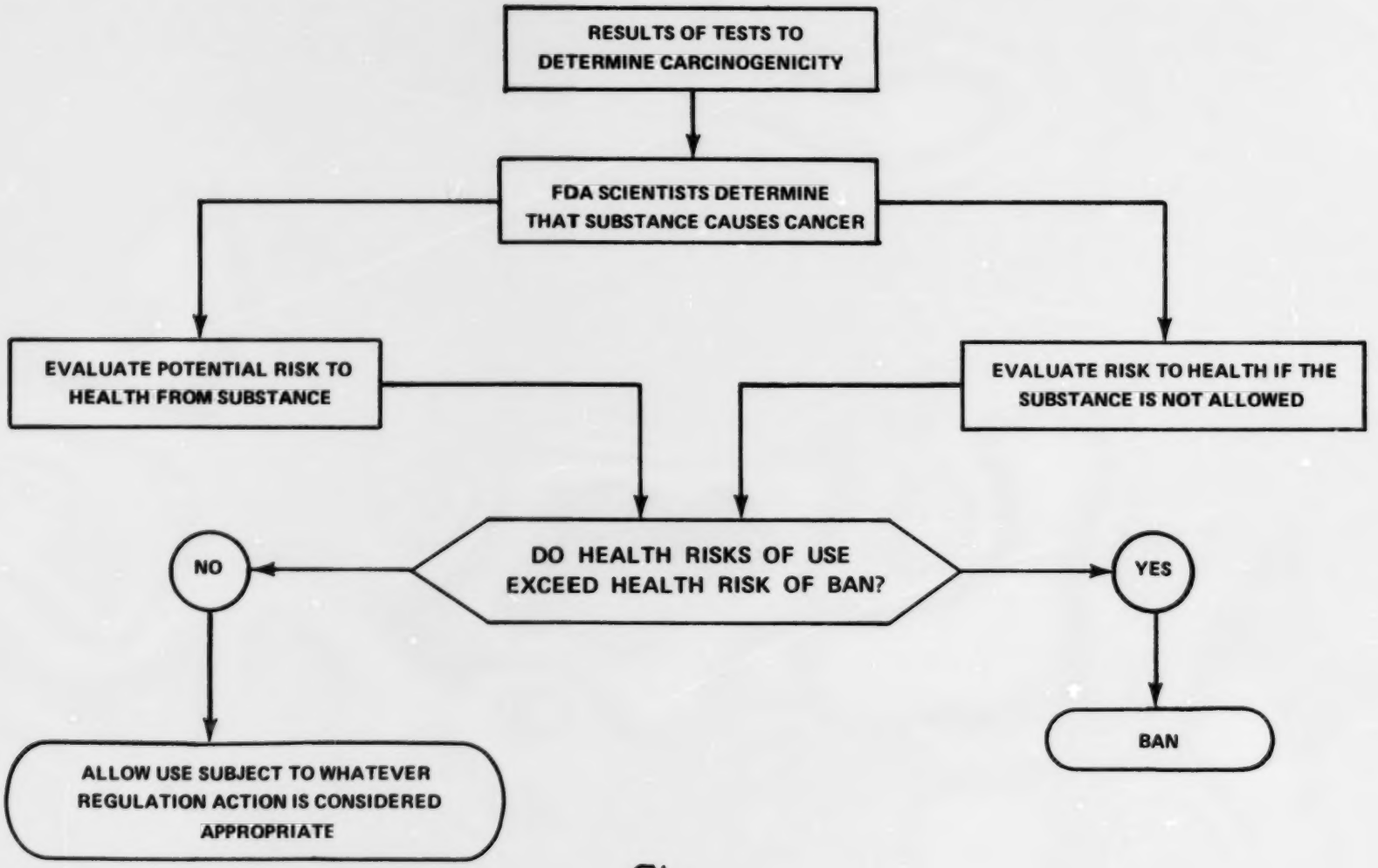
1/CAST is made up of societies for the advancement of agricultural science. CAST reports are prepared by multidisciplinary task forces of scientists nominated by member societies. CAST reports are the responsibility of the task force, not of member societies.

2/"Regulation of Potential Carcinogens in the Food Supply: The Delaney Clause," Council for Agricultural Science and Technology, Report No. 89, June 1981.

EVALUATION OF RISK-RISK


RESULTS OF TESTS TO DETERMINE CARCINOGENICITY
FDA SCIENTISTS DETERMINE THAT SUBSTANCE CAUSES CANCER
EVALUATE POTENTIAL RISK TO HEALTH FROM SUBSTANCE
EVALUATE RISK TO HEALTH IF THE SUBSTANCE IS NOT ALLOWED
DO HEALTH RISKS OF USE EXCEED HEALTH RISK OF BAN?
NO
YES
ALLOW USE SUBJECT TO WHATEVER REGULATION ACTION IS CONSIDERED APPROPRIATE
BAN

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of tests for carcinogenicity, (2) the historical background of carcinogen regulation, (3) the impact of the Delaney Clause, (4) concepts for decisionmaking, and (5) mechanisms for decisionmaking.

CAST identified three possible alternatives to the Delaney Clause:

--Label products with a warning of the possible hazard.

--Establish a level of acceptable risk.

--Maximize net social benefits (make decisions based on whether social benefits exceed social costs).

According to CAST, each of these alternatives has advantages and disadvantages. For instance, labeling would allow consumers freedom of choice. The other two alternatives would allow for a determination that, under certain circumstances, the use of a carcinogen as a food additive could be judged to be acceptable.

The disadvantages, according to CAST, are that accurate estimates of risk to humans cannot now be made, acceptable risk levels would be based on societal considerations not scientific ones, and for the third alternative of maximizing net social benefits, a cost-benefit analysis would have to be made. CAST believes that guidelines for weighing economic effects against cancer risk and health benefits are inadequate.

ALTERNATIVES SUGGESTED BY THE NATIONAL ACADEMY OF SCIENCES

A 1979 report by the NAS Institute of Medicine entitled "Food Safety Policy: Scientific and Societal Considerations" discussed the (1) capabilities to predict carcinogenicity or other toxicity in humans of substances which are added to food, (2) health benefits and risks to individuals from food which contain carcinogenic or other toxic substances, (3) appropriateness of weighing risks against benefits, and (4) relationship between existing Federal food regulatory policy and policy applicable to carcinogenic and other toxic substances.

NAS stated that, in any revised food laws, an assessment of the benefits of food additives should include physical, psychological, and economic factors. NAS recommended that all distinctions between food substances be abolished and that they be regulated based on relative risk--that is, substances found to be hazardous should be categorized into high-, moderate-, and low-risk categories.

According to NAS, FDA should be authorized to ban a high-risk substance regardless of its benefits, especially if a satisfactory substitute is available. However, if no substitute is available and the risk is clearly outweighed in well-defined circumstances by significant benefits that are not available from safer sources, NAS recommends that substances be allowed on the market, with restrictions. Restrictions could include labeling or limits on sales to particular segments of the population.

NAS believes moderate-risk items may be sold with a label indicating a possible risk. A ban could be appropriate if a suitable alternative is available or the substance lacks significant health benefits. According to NAS, low-risk substances should be exempt from special regulatory control.

NAS stated the evaluation of risks and benefits is not subject to precise calculation, however. For many substances the degree of risk is imprecise and benefits are even more uncertain.

The NAS report contained a minority statement that disagreed with several of the majority's recommendations. The minority believed that (1) direct food additives should be regulated differently than other classes of food additives or contaminants, (2) irreversible toxicities, such as cancer, deserve special regulation, and (3) risks from food should be lower than other types of risk. The minority also believed that food additives cannot be classified into risk categories for regulatory purposes. The minority stated that the ability of science to quantify human risk has not advanced far enough since the Delaney Clause was enacted in 1958 to permit a scientifically defensible rationale for this suggestion.

FOOD SAFETY COUNCIL ALTERNATIVES

A 1979 Food Safety Council (FSC) 1/ draft report attempted to devise a comprehensive new approach for making food safety decisions within a well-defined, open, predictable framework.

The report states that two sets of standards could be applied by regulators. One set would identify a level of risk that was judged to be socially unacceptable for each major category of hazards; the other set would establish acceptable minimum benefit requirements. Explicit assessment of risks and benefits would become a part of the proposed new system. Risks are defined as

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1/FSC is an independent, nonprofit organization to encourage cooperation between science, industry, and the public on the question of food safety.

threats to life. Benefits fall into four categories--health, supply, appeal, and convenience.

FSC believes that health risks should be balanced with health benefits. If, after offsetting health risks and benefits, a net health risk still exists, other benefits may offset this. According to FSC, the full use of benefit assessment is restricted to the rare case where the risk is significant and the benefits perceived as important. The goal in this procedure is to arrive at a maximum net social gain--society comes out ahead. The regulatory system should promote the choices that well-informed consumers would make for themselves.

MATTERS FOR CONSIDERATION BY THE CONGRESS

Because of (1) the advances in the ability of analytical detection methods to identify substances at very low levels, (2) the uncertainties about the risk to humans of low levels of carcinogens, and (3) the inflexibility that exists under FDA's present regulatory policy, we believe that the Congress should consider whether the present food safety policy for cancer-causing food additives is still appropriate.

The three options for amending the Delaney Clause (see p. 49) discussed above would require an evaluation of risks and benefits. Based on our discussions with food safety experts and regulatory officials, we believe establishing an acceptable level of risk for a cancer-causing food additive will be a difficult social undertaking. Further, the tools used to measure risk levels are still being developed, and there is disagreement about their accuracy. Criteria for evaluating benefits have been neither defined nor evaluated. A direct balance of risks and benefits is extremely difficult because they are two entirely different considerations. Finally, any attempt to perform a risk-benefit evaluation will involve FDA in a complex series of social judgments. Therefore, when translated into decisions on specific substances, opinions will remain divided.

Any consideration of these alternatives must include an assessment of their impact on food safety. If the Delaney Clause is retained, the current policy of taking more stringent regulatory action against a cancer-causing substance (banning) than against substances causing other toxic health effects (setting tolerances) will continue. Repeal of the Clause and regulation of cancer-causing substances under the general safety clause would result in all food additives being regulated under the same standard. The same scientific criteria would be applied to both carcinogenic and noncarcinogenic food additives. Scientific techniques would be applied in determining the level of risk associated with the use of carcinogenic food additives.

The options identified under the alternative of amending the Delaney Clause are discussed in the framework of carcinogen regulation and, if adopted, would result in different standards for carcinogens and non-cancer-causing substances. (See p. 37.) Therefore, if the Congress chooses to address these options, it should consider whether to apply them equally to carcinogens and non-cancer-causing substances. For example, if the Congress decides that, in the regulation of cancer-causing substances, FDA should consider benefits or determine the health consequences of not using the substance, the Congress should also decide whether non-cancer-causing substances should be similarly regulated.

AGENCY COMMENTS

The Department of Health and Human Services said that this report is an excellent review of the issues and problems concerned with carcinogens in food and food ingredients. According to the Department, the interviews conducted and the opinions solicited are informative and useful, and the consolidation of history, facts, views, and recommendations into a single convenient source should help assure that future decisions concerning the Delaney Clause will be based on adequate detailed knowledge of the subject. The Department added that the administration is considering the alternative approaches that could be adopted for regulating carcinogens in the food supply and that our report would be useful in formating such a policy.

EPA concurred with the general findings and conclusions of this report and added that the findings provide a sound basis for our recommendation that the Congress reexamine the Delaney Clause. The Department of Labor and CPSC provided comments which they believed clarified information in the report.

The four agencies' suggestions to improve the technical precision and accuracy of the report were considered and changes were made where appropriate.

CHAPTER 6

OBJECTIVES, SCOPE, AND METHODOLOGY

Our review of the Delaney Clause was performed at the request of seven Members of Congress. In an October 14, 1978, letter they requested that we report on an FDA-funded study on nitrite at the Massachusetts Institute of Technology. 1/ In addition, they asked us to "review the whole broad question of the effects of the 'Delaney Clause' on the regulatory processes of the federal government" and to provide an "assessment of the extent to which the current law precludes balanced appraisal of carcinogenic risks of public health and well-being."

The Members were particularly interested in (1) public perceptions of the carcinogenic risk from food additives, (2) the science of carcinogenic testing, and (3) alternative decisionmaking concepts which might be used in lieu of the Delaney Clause.

REPORT OBJECTIVES

The Delaney Clause has been the subject of numerous papers, reports, and symposia. Some of these efforts represented years of work by scientists, attorneys, economists, and representatives of other disciplines who had vast experience working in this field. Our intent was not to attempt to repeat these efforts. Instead, we directed our efforts at determining the

- --opinions of experts regarding the perceived impact of the Delaney Clause, the need to delete or modify it, and alternative ways of doing so;
- --public's attitude toward allowing the use of carcinogens in food;
- --social, scientific, and regulatory issues that cause disagreement about the Delaney Clause and the use of food additives that may cause cancer; and
- --alternatives to the Delaney Clause for making decisions about the use of food additives that may cause cancer.

SCOPE AND METHODOLOGY

We reviewed legislation, legislative histories, and numerous articles and studies on the Delaney Clause. We met with knowledgeable individuals at the Congressional Research Service, the

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1/See "Does Nitrite Cause Cancer? Concerns About Validity of FDA-Sponsored Study Delay Answer" (HRD-80-46, Jan. 31, 1980).

Office of Technology Assessment, NCI, NAS, and FSC in the Washington, D.C., area. In addition, during the review we interviewed more than 75 food safety experts, including scientists and representatives from food and chemical companies and trade associations throughout the United States.

We also interviewed several past and present FDA officials and reviewed Federal Register notices and other documents to determine how often and under what circumstances the Delaney Clause has been invoked. We attempted to identify the advantages and disadvantages of using a no-risk policy in regulating cancer-causing food additives.

To identify how other Federal agencies regulate carcinogens and the advantages and disadvantages of other approaches, we conducted 17 interviews and reviewed pertinent legislation, regulations, and other documents at EPA, OSHA, and CPSC. These agencies, as well as FDA, are the principal Federal agencies responsible for regulating carcinogens in the food supply, environment, workplace, and consumer products. The officials with whom we spoke worked in the areas of toxicology, chemistry, pathology, mathematics, and epidemiology. We also spoke with attorneys and administrators at these agencies. In addition, we performed work at the Department of Agriculture, which does not typically regulate carcinogens in meat, poultry, and egg products, but rather enforces regulations established by EPA and FDA.

We requested that CAST convene a group of its experts to review scientific and regulatory issues and possible alternatives to the Delaney Clause. CAST later issued a report in response to our request. (See p. 53.)

Public opinion polls

We obtained information on the public's attitudes by researching prior public opinion polls. We requested the Congressional Research Service to perform an informal review of its computerized data banks. We also worked with our Audit Reference Service Library to identify any relevant polls, and we reviewed literature and performed research at the Library of Congress.

To identify federally sponsored polls, we met with FDA polling experts and talked to Department of Agriculture personnel responsible for agency polls. We contracted with the University of North Carolina for a computerized data retrieval search for prior Harris Organization polls. Finally, during our interviews with food safety experts, we inquired whether they were familiar with any relevant polls or if their organizations had contracted for their own polls.

We did not review the designs, implementations, or analyses of the polls cited in the report. We did not use age, income, religious, or other categories of respondents gathered by the pollsters because we did not think that these data were relevant for our purposes.

Expert interviews

Our review of the literature established that Delaney Clause experts fell into four categories--(1) consumer groups, (2) industry-trade associations and food and chemical companies, (3) biomedical researchers, and (4) former FDA Commissioners and General Counsels. There are four former General Counsels and six former FDA Commissioners who served after enactment of the Delaney Clause in 1958. We interviewed all the former General Counsels and all but one former Commissioner, who was unable to meet with us.

From the numerous reports and papers published on Delaney Clause issues, we gathered a list of names for the first three groups, including authors of articles and individuals cited in reports. We asked knowledgeable individuals at FDA, NCI, FSC, the Office of Technology Assessment, and the Congressional Research Service and a former consumer representative to review the lists and suggest experts whom they believed we should interview. We collated the names and selected the experts who had been picked by most of these individuals. We selected and interviewed individuals who represented a variety of disciplines--epidemiology, toxicology, pathology, and food science and who were located in the New York and Washington, D.C., areas, California, and the Midwest. In addition, we interviewed eight knowledgeable industry experts whose names were provided to us by an executive of McCormick and Company.

We developed a standard format for our interviews. Interviews were recorded and transcribed. We could not define the universe of experts, and because a statistically valid sample would have required far more than the 50 interviews we conducted, no statistically valid projections can be made from our data. We included the four largest food companies and the five largest manufacturers of food additives in an effort to ensure that the opinions obtained were representative of the industry.

Since the Delaney Clause is a policy question, food and chemical companies are not required to maintain records on food additive development. Thus, no records were available to substantiate the effect of the Delaney Clause on innovation or development of new food additives. Only anecdotal evidence was available.

FOOD SAFETY EXPERTS

INTERVIEWED BY GAO

Name and position	Affiliation
Former FDA Commissioners	
Dr. Jere Goyan, Dean, School of Pharmacy	University of California San Francisco
Dr. Alexander Schmidt Vice Chancellor	University of Illinois Medical Center
Dr. Charles Edwards President	Scripps Clinic and Research Foundation
Dr. Herbert L. Ley, Jr. Medical Consultant	Ley Consultants
Dr. James L. Goddard Medical Consultant	
Former FDA General Counsels	
Mr. Richard Cooper	Williams and Connally
Mr. Richard Merrill Dean	University of Virginia Law School
Mr. Peter B. Hutt	Covington and Burling
Mr. William Goodrich President	Institute of Shortening and Edible Oils
Biomedical Researchers	
Dr. Roy Albert Professor and Deputy Director	Institute of Environmental Medicine, New York University Medical Center
Dr. Ernst Wynder President	American Health Foundation
Mr. Richard Klarberg Counsel	American Health Foundation
Dr. Bruce Ames Professor of Biochemistry	University of California at Berkeley

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Name and position	Affiliation
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Dr. Richard Bates Senior Toxicologist/Pathologist	Clement Associates
Dr. Joseph Rodericks Science Director (Risk and Safety Assessment)	Clement Associates
Dr. William Darby President	The Nutrition Foundation
Dr. Joshua Lederberg President	Rockefeller University
Dr. William Lijinsky Director, Chemical Carcinogens Program	Frederick Cancer Research Center, National Cancer Institute
Dr. Joyce McCann Biomedical Division	Lawrence Berkeley Laboratory
Dr. Norton Nelson	Institute of Environmental Medicine, New York University Medical Center
Dr. Bernard Oser President	Oser Consultants
Dr. Richard Ford Vice-President	Oser Consultants
Dr. Frank Rauscher Senior Vice-President for Research	American Cancer Society
Dr. Irving Selikoff Director of the Environmental Sciences Laboratory	Department of Community Medicine, Mt. Sinai School of Medicine, City University of New York
Dr. Robert Squire Associate Professor of Pathology and Comparative Medicine	The Johns Hopkins University School of Medicine

Name and position	Affiliation
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Consumer Groups	
Dr. Michael Jacobson Executive Director	Center for Science in the Public Interest
Ms. Ellen Haas Director, Consumer Division	Community Nutrition Institute
Mr. Rodney Leonard Executive Director	Community Nutrition Institute
Ms. Ruth Simon Staff member	Consumer Federation of America
Ms. Ann Avery Staff member	Consumer Federation of America
Mr. Mark Silbergeld Staff member	Consumers Union
Dr. Joseph Highland Chairman, Toxic Chemicals Program	Environmental Defense Fund
Dr. Sidney Wolfe President	Public Citizen, Inc.
Mr. William B. Schultz Attorney	Public Citizen's Litigation Group
Trade Associations	
Dr. William McCarville Director of Environmental Affairs	American Industrial Health Council
Dr. Leonard Guarraia Director of Government Affairs	American Industrial Health Council

Name and position	Affiliation
Ms. Michele F. Crown General Counsel	American Meat Institute
Dr. John Birdsall Director, Scientific Activities	American Meat Institute
Dr. Forrest Dryden Assistant Director, Scientific Activities	American Meat Institute
Dr. Geraldine Cox Vice President, Technical Director	Chemical Manufacturers Association
Mr. Randy Schumocher Director, Regulatory Affairs	Chemical Manufacturers Association
Mr. Sherwin Gardner Vice-President, Science and Technology	Grocery Manufacturers Association
Dr. Ira Sommers Executive Vice-President	National Food Processors Association
Dr. Richard Hagen Vice-President and Manager, Washington Laboratories	National Food Processors Association
Dr. Lowrie M. Beacham Special Advisor to the President	National Food Processors Association
Food and Chemical Companies	
Mr. Dick Kasperson Vice-President, Corporate Regulatory Affairs	Abbott Laboratories
Mr. Mike Foley Director, Federal Regulatory Affairs	Abbott Laboratories
Dr. Roy Tjepkema Director and General Manager Research Center and Quality Control Department	Beatrice Foods Company
Dr. D. M. Graham Director, Central Research	Del Monte Corporation

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Dr. John Kirschman Vice-President, International Research	General Foods Corporation
Dr. Robert DiMarco Vice-President, National Research	General Foods Corporation
Mr. A. S. Clausi Vice-President, Corporate Research	General Foods Corporation
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Dr. Roland Beers, Jr. Vice-President, Research Affairs	Miles Laboratories
Mr. Adrien L. Ringuette Secretary and General Counsel	Miles Laboratories
Mr. Robert Harness Director, Government Affairs	Monsanto Company
Mr. K. Warren Easley Director, Regulatory Affairs	Monsanto Company
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Mr. Walter Meyer Associate Director, Food Products Division	Proctor and Gamble Company
Dr. Robert H. Coots Associate Director, Human and Environmental Safety Division	Proctor and Gamble Company
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Mr. George Meyding Governmental Relations	Stauffer Chemical Company
Dr. Richard Greenberg Former Vice-President, Science and Technology	Swift and Company
Dr. Robert Smith Vice-President, Research and Development	Swift and Company
Mr. James Noonan Vice-President and General Manager, Color Division	Warner Jenkinson Unit, 7-Up
Mr. Doug Aller Manager, Government Affairs	Warner Jenkinson Unit, 7-Up

GENERAL CLASSIFICATION OF TESTS AVAILABLE TO DETERMINE PROPERTIES RELATED TO CARCINOGENICITY

Method	Organism used	Time required	Basis for test	Result	Conclusion, if result is positive
Molecular structure analysis	"Paper chemistry" Basic laboratory tests	Days Weeks	Chemicals with like structures interact similarly with DNA	Structure resembles (positive) or does not resemble (negative) structure of known carcinogen	Chemical may be hazardous That determination requires further testing
Short-term tests	Bacteria, yeast, cultured cells, intact animals	Generally few weeks (range 1 day to 8 months)	Chemical interaction with DNA can be measured in biological systems	Chemical causes (positive) or does not cause (negative) a response known to be caused by carcinogens	Chemical is recognized as a potential carcinogen
Bioassay	Intact animals (rats, mice)	2 to 5 years	Chemicals that cause tumors in animals may cause tumors in humans	Chemical causes (positive) or does not cause (negative) increased incidence of tumors	Chemical is recognized as a carcinogen in that species and as a potential human carcinogen
Epidemiologic	Humans	Months to lifetimes	Chemicals that cause cancer can be detected in studies of human population	Chemical is associated (positive) or is not associated (negative) with an increased incidence of cancer	Chemical is recognized as a human carcinogen

Source: Office of Technology Assessment, "Assessment of Technologies for Determining Cancer Risks From the Environment," June 1981, p. 114.

APPENDIX II

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APPENDIX IV

FEDERAL REGULATION OF CANCER-CAUSING SUBSTANCES

	Administered by	Type of substances regulated	Specific procedures for regulating carcinogens	If this does not apply, how are carcinogens regulated?	Benefit-risk analysis or consideration of factors other than safety	Discretion in regulating
Federal Food, Drug, and Cosmetic Act food provisions	FDA, Dept. of Health and Human Services	Food additives, naturally occurring substances, food contaminants, substances that are prior sanctioned and generally recognized as safe, color additives, and residues of animal drugs.	Yes, for food additives, color additives, residues of animal drugs.	For other sections, criteria are general safety or reasonable expectation that use will not be harmful.	Risks dominate; no such analysis permitted for carcinogenic food and color additives and residues from animal drugs; if a naturally occurring substance is carcinogenic, the substance's health benefits and the economic impact of a ban may be weighed against the health risk; if a food contaminant is carcinogenic, the technological feasibility of removing the contaminant and the available food supply are weighed against the health risk.	Carcinogenic food and color additives, and food with carcinogenic residues of animal drugs must be banned; otherwide discretion is permitted.
Toxic Substances Control Act	EPA	Substances such as foods, drugs, cosmetics, tobacco are not covered; all non-excluded substances are covered, but if other acts cover such substances, those acts take precedence.	Carcinogenic and certain other substances are to receive priority attention; a ruling must be made on carcinogens within a specified time; but regulatory action is based on toxicity.	Toxicity; cancer regarded as a priority class of toxicity.	Explicitly required by the act.	All regulatory actions are at the discretion of EPA.
Clean Air Act; Federal Water Pollution Control Act; Safe Drinking Water Act; Federal Insecticide, Fungicide, and Rodenticide Act	EPA	Pollutants in the respective areas of the environment.	No	As environmental pollutants posing danger to public health; toxicity.	Permitted.	All regulatory actions are at the discretion of EPA.
Consumer Product Safety Act	CPSC	Substances used by consumers (at home, in recreation, etc.).	No	As hazardous products, or imminent hazards.	Explicitly required by the act.	All regulatory actions are at the discretion of CPSC.
Federal Hazardous Substances Act	CPSC	Hazardous substances (in effect, it primarily covers household products).	No	As hazardous substances; toxicity is criterion.	Not explicitly mentioned; has been interpreted as allowing it, and CPSC uses such analyses.	Banning is at the discretion of CPSC; certain labeling requirements are nondiscretionary.
Occupational Safety and Health Act	OSHA, Dept. of Labor	Hazardous substances in the workplace.	No; implementing regulations require the identification, classification, and prioritization of carcinogens.	As toxic substances.	Permitted by the act; required by the implementing regulations.	Yes.

Primary source: Office of Technology Assessment, "Cancer Testing Technology and Saccharin," October 1977, p. 16.

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APPENDIX V

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

OCT 22 1981

Mr. Gregory J. Ahart
Director, Human Resources
Division
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Ahart:

The Secretary asked that I respond to your request for our comments on your draft report entitled, "Regulation of Cancer-Causing Food Additives--Is It Time for a Change?" The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,

Richard P. Kusserow
Inspector General

Enclosure

APPENDIX V

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GENERAL ACCOUNTING OFFICE'S DRAFT REPORT "REGULATION OF CANCER-CAUSING FOOD ADDITIVES--IS IT TIME FOR A CHANGE?," DATED SEPTEMBER 21, 1981

General Comments

The draft report is an excellent review of the issues and problems concerned with carcinogens in food and food ingredients. The interviews conducted and the opinions solicited are informative and useful. The consolidation of history, facts, views and recommendations into a single convenient source should help assure that whatever decisions are made in the future concerning the Delaney Clause will be based on adequate detailed knowledge of the subject. The Administration is presently considering the alternative approaches that could be adopted for regulating carcinogens in the food supply. This document will be useful in formulating such a policy. Our comments at this time will, therefore, only address errors in stating the statutory requirements, FDA's interpretation of those requirements, and technical corrections.

GAO note: Corrections to the text of the report were considered and made where appropriate.

APPENDIX VI

U.S. Department of Labor

Assistant Secretary for
Occupational Safety and Health
Washington, D.C 20210

OCT 26 1981

Gregory J. Ahart
Director, Human Resources Division
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Ahart:

Secretary Donovan has asked me to respond to your letter of September 21, 1981, requesting comments on the draft General Accounting Office report entitled "Regulation of Cancer Causing Food Additives--Is it Time for a Change?" The Department's response is enclosed.

The Department of Labor appreciates the opportunity to comment on this report.

Sincerely,

Thorne G. Auchter
Assistant Secretary

Enclosure

GAO note: Corrections to the text of the report were considered and made where appropriate.

APPENDIX VII

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OCT 23 1981

OFFICE OF
POLICY AND RESOURCE MANAGEMENT

Mr. Henry Eschwege
Director
Community and Economic Development Division
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Eschwege:

The Environmental Protection Agency (EPA) has reviewed the General Accounting Office (GAO) draft report entitled "Regulations of Cancer-Causing Food Additives -- Is It Time for a Change?"

The report discusses the Delaney Clause of the 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act, which directs the Food and Drug Administration (FDA) to ban the use of cancer-causing food additives. According to the draft report, food safety experts believe the Delaney Clause should be changed because of its inflexibility; however, they disagree on alternative regulations to the present statute.

The GAO report also points out that the requirements of the Delaney Clause are inconsistent with the statutes mandating the approaches used by EPA, the Consumer Product Safety Commission (CPSC) and the Occupational Safety and Health Administration (OSHA). For this reason and also because of advances in scientific methodology, uncertainties about the human risks from low-level carcinogens and the inflexibility that exists under the Delaney Clause, GAO recommends that Congress reexamine the Delaney Clause.

EPA concurs with the general findings and conclusions that GAO has reached in its analysis. EPA also concurs that these findings provide a sound basis for GAO's recommendation that Congress reexamine the Delaney Clause.

GAO has also specifically recommended that Congress consider three possible approaches for amending the Delaney Clause:

1. Set an acceptable level of risk;

2. Compare health benefits of using a carcinogen with health risks of not using it; and

3. Compare risks and benefits.

Under various circumstances, EPA has used all three approaches in regulating pollutants under its different statutes. Other Federal agencies, in particular, OSHA and CPSC, have also used some of the above approaches in various regulatory actions. All three alternatives would require a case-by-case assessment of risk. None of these three alternatives would conflict with EPA's regulatory approach to carcinogens.

Public Law 96-223 requires EPA to submit comments on the draft report so that GAO may consider our statements prior to publication of the final report. Technical comments are enclosed.

We appreciate very much the opportunity to comment on this GAO draft report.

Sincerely yours,

Joseph A. Cannon
Acting Associate Administrator
for Policy and Resource Management

Enclosure

GAO note: Corrections to the text of the report were considered and made where appropriate.

APPENDIX VIII

U.S. CONSUMER PRODUCT SAFETY COMMISSION

WASHINGTON, D.C. 20207

October 23, 1981

OFFICE OF THE
GENERAL COUNSEL

Mr. Gregory J. Ahart
Director, Human Resources Division
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Ahart:

Thank you for this opportunity to comment on the draft report entitled "Regulation of Cancer-Causing Food Additives -- It is Time for a Change." The draft report discusses various issues relating to the Food and Drug Administration's regulation of cancer-causing food additives and contains some information on how the Consumer Product Safety Commission regulates cancer-causing substances in consumer products.

We have no general comments on or problems with the report. Our only comment concerns page 56 of the draft report where the text mischaracterizes the Commission's actions regarding the chemical flame-retardant Tris as a "ban." In fact, the Federal Hazardous Substances Act (FHSA) itself automatically bans, without agency action, any children's article (such as children's sleepwear) which contains a hazardous substance. The Commission merely evaluated technical information and determined that children's sleepwear treated with the chemical flame-retardant Tris was a hazardous substance within the meaning of the Act because Tris was an animal carcinogen that could be absorbed through the skin. Since there was no agency regulation, the Commission's determination regarding Tris may, of course, be tested in an enforcement proceeding. We suggest that the Commission's action regarding Tris be rephrased as an enforcement interpretation under the FHSA. In addition, the Commission has not banned benzene in consumer products; the Commission proposed to ban benzene in certain products and then withdrew the proposal because of the declining use of benzene in these products. Furthermore, the Commission has not banned vinyl chloride or asbestos in consumer products in general. The Commission banned two asbestos containing

APPENDIX VIII

products: patching compounds and artificial emberizing materials; the Commission banned self-pressurized products containing vinyl chloride monomer.

I hope this information is helpful.

Sincerely,

Margaret A. Freeston

Margaret A. Freeston
Acting General Counsel

GAO note: Page reference in this letter may not correspond to the page number in the final report.

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